EXHIBIT 12

Statistical Reviewer Briefing Document for the Advisory Committee

NDA20-998
Name of Drug: Celebrex (celebrex)
Applicant: G. D. Searle
Indication: Lower Upper Gastrointestinal Adverse Events Compared with NSAID
Documents Reviewed: Statistical Section of NDA20998 Dated 06/14/00 by CDER
Medical Reviewer: Lawrance Goldkind, M.D., James Witter, MD
Reviewer: Hong Laura Lu, Ph.D.
Date of Review: 6/00-

I. Background

This NDA is submitted to support the claim that celebrex causes lower incidence of clinically significant upper gastrointestinal adverse events (CSUGIE) compared to ibuprofen and diclofenac during chronic administration (up to 12 months) in patients with osteoarthritis (OA) or rheumatoid arthritis (RA). This review focuses on the two phase III studies (Studies 035 and 102).

II. Study Protocol (Study 035 and Study 102)

Study 035 was a randomized, double-blind, parallel group, multicenter study designed to compare the incidence of CSUGIEs associated with celebrex 400 mg BID to that associated with ibuprofen 800 mg TID in patients with OA or RA. Study 102 was identically designed as Study 035 except that the active control group was diclofenac 75 mg BID.

The treatment period for both studies was defined as the 52-week interval during which study medication was taken or until the trial was officially concluded, whichever occurred first. Patients were evaluated at Week 4, Week 13, Week 26, Week 39, Week 52 and the end of the treatment.

The primary comparison was the incidence of CSUGIEs associated with celebrex 400 mg BID to that associated with ibuprofen 800 mg TID and diclofenac 75 mg BID. Time-to-event analysis was performed to assess the difference between groups in the CSUGIE rate distribution across time. CSUGIE occurring within 2 days after first dosing or beyond 2 days after last dosing was censored and not included in these analyses. The log-rank test was used to compare the survival curves of the two treatment groups (celebrex vs. the NSAID groups) with respect to this primary outcome variable. Patients who withdrew from the study because of reasons other than incidence of CSUGIE were censored at the time of withdrawal. Patients who complete the study without a CSUGIE were censored at the final visit. Two primary treatment comparisons were performed: celebrex vs. ibuprofen and celebrex vs. diclofenac. A stepwise procedure was used to strongly control the type-I error. In this procedure, the first step was to test the overall hypothesis whether celebrex and the pooled NSAIDs were different. If the test is not significant, the null hypothesis is retained and the procedure stops. If the test is significant, the second step will be the pairwise tests between celebrex and each of the two NSAIDs. Celebrex will be claimed to be different from an NSAID if both overall and pairwise comparisons of celebrex vs. that NSAID are

significant. Each test was performed at level α. No α adjustment was needed for each test. Two primary endpoints were analyzed. One was based on the traditional definition of CSUGIE and the other alternative one was proposed by FDA. To control the type-I error rate, a pre-specified stepwise procedure was used. The first step was to test treatment difference based on the traditional definition of endpoint. If it is significant, then test on the alternate endpoint. If both steps show significance, celebrex will be claimed to be different from the NSAID(s) on both endpoints. If only the first step shows significance, celebrex will be claimed to be different from the NSAID(s) on the traditional endpoint.

Potential risk factors such as age and history of peptic ulcer, for the development of a clinically significant UGI adverse event were identified prior to analysis and the proportional hazard model was used to assess the significance of these factors and their impact on the effect of treatment on outcome. Mean values and their confidence intervals for the Patient's Global Assessment of Arthritis, the Patient's Assessment of Arthritis Pain, and Health Assessment Questionnaire (HAQ) were tabulated. Information for Incidence of withdrawal due to lack of arthritis efficacy was provided.

All analyses were carried out on the intent-to-treat cohort, which consisted of all randomized patients from both studies who received at least one dose of study medication.

The sample size determination was based on the assumption that the probability for experiencing a CSUGIE was 0.3% per year with celebrex and 1.2% per year with NSAIDs as a group. To detect this difference with at least 90% power at a 5% significance level (two-sided test) and assuming a withdrawal rate of 35%, a sample size of 8,000 patients (4,000 patients for the celebrex and 2000 for each NSAID group) was sufficient to obtain approximately a total of 40 clinically significant UGI adverse events.

III. Study Report for Studies 035 and 102

III.1 Patient Disposition

A total of 8059 patients were randomized: 4031 to the celebrex 400 mg BID group, 2019 to the diclofenac 75 mg BID group, and 2009 to the ibuprofen 800 mg TID group. Ninety-one (91) patients were determined never to have taken any study medication. The majority of withdrawals in all treatment groups were due to adverse events (22.7% in celebrex group, 27.1% in diclofenac group and 23.2% in ibuprofen group), treatment failure (17.3% in celebrex group, 15.5% in diclofenac group and 23.0% in ibuprofen group), or protocol noncompliance (14.7% in celebrex group, 9.9% in diclofenac group and 18.4% in ibuprofen group). Detailed results for patient disposition are presented in Table 1 below.

Table 1. Patient Disposition

	Celebrex	Diclofenac	Ibuprofen
Overall	3987	1996	1985
Completed Study	1779(44.6%)	939(47.0%)	691(34.8%)
Complete With GI AE	401	257	187
Withdrawn	2208(55.4%)	1057(53.0%)	1294(65.2%)
Reason for Withdrawal:			
Lost to Follow-Up	0(0.0%)	0(0.0%)	0(0.0%)
Pre-Existing Violation	27(0.7%)	11(0.6%)	12(0.6%)
Protocol Noncompliance	585(14.7%)	197(9.9%)	365(18.4%)
Treatment Failure	691(17.3%)	309(15.5%)	456(23.0%)
Adverse Event	905(22.7%)	540(27.1%)	461(23.2%)

III.2 Demographics

Baseline demographic characteristics, vital signs and GI risk factors are generally balanced between treatment groups. Detailed demographic information is summarized in Tables a1-a4 in Appendix A.

III.3 Sponsor's Analysis and Results of UGI Safety Results (reviewer's comments and analyses are in Section IV)

III.3.1 CSUGIE results for entire study period

A total of 44 events were found to represent CSUGIE throughout the entire study. Twenty events (20) occurred on celebrex treatment, 11 on diclofenac, and 13 on ibuprofen. Among these events, a total of 6 were considered censored (3 in the celebrex group, 1 in the diclofenac group, and 2 in the ibuprofen group) due to the timing of their occurrence (occurred within 2 days after first dosing or beyond 2 days after last dosing).

As shown in Figure 1, the uncensored events were shown to continue to accrue in the celebrex group at a generally steady rate through the end of the study. In contrast, only one uncensored event occurred in the diclofenac group after 182 days, and none occurred in the ibuprofen group. The curves for the two NSAIDs therefore become essentially flat after this time, with the result that the end points of the three curves were similar by the end of the study. None of the differences in time to event among the treatment groups were statistically significant. Summary results for CSUGIE were presented in Table 2.

Figure 1. Kaplan-Meier Estimator for CSUGIE Incidence

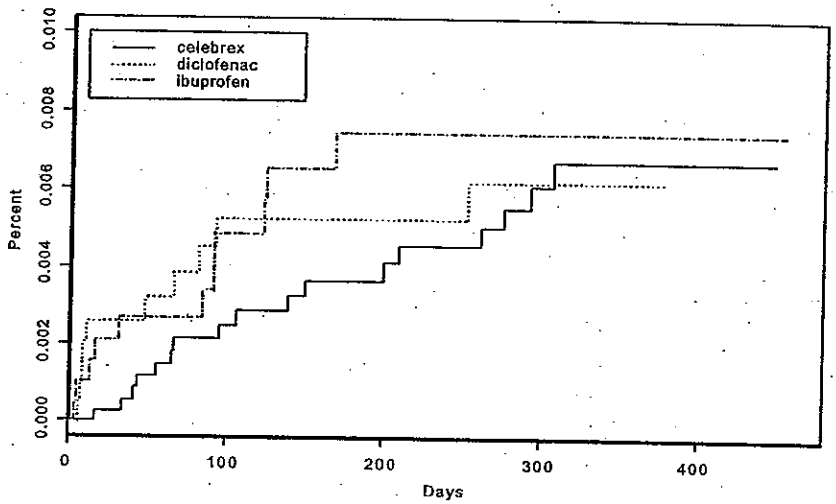

Table 2. Summary of CSUGIE Incidence

	Celebrex 400 mg BID	Diclofenac 75 mg BID	Ibuprofen 800 mg TID	Log-Rank P Values for Celebrex vs. Diclofenac	Ibuprofen	Both
No. of Patients	n=3987	n=1996	n=1985			
No. of CSUGIE						
Uncensored	17	10	11			
Censored*	3	1	2			
Total	20	11	13			
Week 52 crude rate	0.43%	0.50%	0.55%	0.640	0.414	0.450

*Occurred before 48 hours after midnight of the first dose day or more than 48 hours after midnight of the last dose day (unless occurred within two weeks after last dose and was determined by GEC to be treatment-related).

A total of 35 events were found to satisfy the alternate definition of CSUGIE. No statistical analysis was performed since the lack of statistical significance in the results of CSUGIE with traditional definition. However, the event rates with alternate definition followed the same trend as that with traditional definition. The results are presented in Table 3 below.

Table 3. Summary of CSUGIE Incidence: Alternate Definitions

	Celebrex 400 mg BID (n=3987)	Diclofenac 75 mg BID (n=1996)	Ibuprofen 800 mg TID (n=1985)
No. of CSUGIEs			
Uncensored	17	5	9
Censored	2	1	1
Total	19	6	10
Week 52 crude rate	0.43%	0.25%	0.45%

III.3.2 Post-Hoc Safety Analyses

III.3.2.a Analysis for the first 6 months

The sponsor also conducted analysis for CSUGIE with only the first 6 months data based on the argument that the large dropout rate in the later stage of the study depleted high-risk patients. The 6 months' data showed that the CSUGIE rates of ibuprofen and diclofenac (0.55% and 0.45%, respectively) were numerically higher than that of celebrex (0.28%), but the difference did not reach statistical significance (p=0.092). The results are summarized in Table 5 below.

Table 5. Summary of CSUGIE Incidence - First Six Months

	Celebrex 400 mg BID	Diclofenac 75 mg BID	Ibuprofen 800 mg TID	Log-Rank P Values for Celebrex vs.		
				Diclofenac	Ibuprofen	Both
	n=3987	n=1996	n=1985			
No. of CSUGIEs						
Uncensored	11	9	11			
Censored*	2	0	2			
Total	13	9	13			
Week 26 crude rate	0.28%	0.45%	0.55%	0.264	0.073	0.092

*Occurred before 48 hours after midnight of the first dose day or more than 48 hours after midnight of the last dose day (unless occurred within two weeks after last dose and was determined by GEC to be treatment-related).

III.3.2.b Subgroup analysis

Analysis for CSUGIE was also conducted for non-aspirin users with the argument that aspirin was an independent cause for CSUGIEs. Among non-aspirin users, celebrex did not show statistically significant (p=0.185) reduction in CSUGIEs over the entire study period. However, with only the first 6 months data, the CSUGIE rate of celebrex was numerically lower than that of ibuprofen and diclofenac with a p-value less than 0.05. The detailed results for the entire study period and the first 6 months are presented in Table 6 below.

Table 6. CSUGIE Incidence in Patients not Taking Aspirin

	Celebrex 400 mg BID	Diclofenac 75 mg BID	Ibuprofen 800 mg TID	Log-Rank P Values for Celebrex vs.		
				Diclofenac	Ibuprofen	Both
Entire Study Period						
	n=3105	n=1551	n=1573			
No. of CSUGIEs						
Uncensored	8	4	10			
Censored*	1	0	1			
Total	9	4	11			
Week 52 crude rate	0.26%	0.26%	0.64%	0.972	0.037	0.185
First 6 Months						
	n=3154	n=1567	n=1602			
No. of CSUGIEs						
Uncensored	5	4	10			
Censored*	1	0	1			
Total	6	4	11			
Week 26 crude rate	0.16%	0.26%	0.62%	0.476	0.005	0.037

*Occurred before 48 hours after midnight of the first dose day or more than 48 hours after midnight of the last dose day (unless occurred within two weeks after last dose and was determined by GEC to be treatment-related).

III.3.2.c Analysis for Combined CSUGIE/GDU Events

The sponsor also conducted analysis for combined CSUGIE/gastrodudenal ulcer (GDU) events. A total of 111 CSUGIEs/GDUs occurred over the entire study period: 46 in the celebrex group, 27 in the diclofenac group, and 38 in the ibuprofen group. The cumulative event rates were lower over the entire study period for celebrex than for the NSAID comparators pooled (p=0.040) and ibuprofen (p=0.017). When only patients not taking aspirin were included in the analysis, the celebrex event rate over 52 weeks was lower than the rate for the NSAIDs pooled (p=0.020) and the rate for ibuprofen (p<0.001). The detailed results are included in Table 7 below.

Table 7. Summary of CSUGIE/GDU Incidence

	Celebrex 400 mg BID	Diclofenac 75 mg BID	Ibuprofen 800 mg TID	Log-Rank P Values for Celebrex vs. Diclofenac	Ibuprofen	Both
All Patients						
	n=3987	n=1996	n=1985			
No. of CSUGIEs						
Uncensored	43	26	36			
Censored*	3	1	2			
Total	46	27	38			
Week 52 crude rate	1.05%	1.30%	1.76%	0.296	0.017	0.040
Patients not Taking Aspirin						
	n=3105	n=1551	n=1573			
No. of CSUGIEs						
Uncensored	21	10	28			
Censored*	1	0	1			
Total	22	10	29			
Week 52 crude rate	0.68%	0.64%	1.78%	0.992	<0.001	0.020

*Occurred before 48 hours after midnight of the first dose day or more than 48 hours after midnight of the last dose day (unless occurred within two weeks after last dose and was determined by GEC to be treatment-related).

III.3.2.d Data Imputation

The sponsor argued that since GI adverse events represent risk factors for events, withdrawals due to GI adverse events represent loss of patients at risk. Based on this argument, the sponsor calculated incidences for patients who did/did not experience GI symptoms and who continued in the study, and these incidences were then applied to patients who discontinued with/without GI symptoms and the expected numbers of CSUGIE in these two patient groups were estimated. Details for imputation and calculation for CSUGIE incidence are in Appendix B.
Table 8 below shows the estimated CSUGIE numbers and rates after imputation for the withdrawal group. The p-values in Table 8 were generated by Fisher's exact test on the expected numbers of CSUGIE.

Table 8. Crude Incidence Rates of CSUGIEs with Imputation for Withdrawals

	Celebrex 400 mg BID (n=3987)	Diclofenac 75 mg BID (n=1996)	Ibuprofen 800 mg TID (n=1985)	Celebrex vs. Diclofenac	Celebrex vs. Ibuprofen
First six months					
CSUGIE	15 (0.4%)	16 (0.8%)	16 (0.8%)	p=0.036	p=0.035
Entire study					
CSUGIE	25 (0.6%)	23 (1.2%)	21 (1.1%)	p=0.044	p=0.084

III.3.3 Efficacy Analyses

Efficacy of the three treatment groups were assessed by patient's global, patient's assessment of arthritis pain, time to withdrawal due to lack of arthritis efficacy, and HAQ. The three treatment groups were numerically comparable in efficacy results. The means and confidence intervals are reported in Tables a5-a8 Appendix A.

IV. Reviewer's Comments

IV.1 Imputation of CSUGIE Rates

The sponsor's rationales for imputation of CSUGIE were that 1) the patients with GI adverse events would have higher probability to develop a CSUGIE over the treatment duration (see Table 2 in Appendix B) and 2) higher withdrawal incidence with earlier withdrawal time in the diclofenac group were observed (see Table 1 in Appendix B), an estimation for the entire study period without adjustment for these informative censoring would not be appropriate for interpretation.

The above two reasons are not valid based on this reviewer's analysis. Table 9 displays the time to GI AEs (mild-moderate-severe GI AE, moderate-severe GI AE and severe GI AE) and time to CSUGIE for patients who had both GI AE and CSUGIE. A phenomenon observed in this Table is that, for most patients, the time to GI AEs and time to CSUGIE are identical. For example, among the 8 patients who had both severe GI AE and CSUGIE, 6 of them developed the GI AE and CSUGIE on the same day, one of them developed CSUGIE in two days after GI AE, and the other one had CSUGIE 20 days before GI AE. So instead of being a pre-event that predicts CSUGIE, most GI AEs were actually the sentinel symptoms of CSUGIE themselves, providing no predictive value at all (see Dr. Goldkind's review for further comments). As suggested by the medical reviewer, this reviewer recalculated the relative risk of the GI AE group vs. non-GI AE group by defining predictive GI AEs as those happened more then 48 hours before a CSUGIE, so that those GI AEs happened within 48 hours of a CSUGIE are excluded from GI AE groups. The results presented in Table 10 show that the GI AE groups (mild-moderate-severe, moderate-severe and sever GI AE) actually have lower risks than the non-GI AE group. So the sponsor's rationales for imputation of the CSUGIEs is not supported by the data.

Table 9. Time to GI AEs and Time to CSUGIE in Patients with Both GI AE and CSUGIE

Patient #	Treatment	T_MD-MT-SV*	T_MT-SEV**	T_SEV***	T_CSUGIE****
12391	celebrex	261	.	.	261
10761	celebrex	307	307	307	307
20349	celebrex	199	.	.	199
11159	celebrex	43	63	63	43
10012	celebrex	12	.	.	276
11153	celebrex	67	67	67	67
11341	celebrex	10	150	150	150
12176	celebrex	139	139	.	139
20035	declofenac	6	6	.	6
10032	declofenac	66	66	.	66
10193	declofenac	8	8	8	8
10294	declofenac	7	7	7	9
20398	declofenac	41	41	.	49
11559	declofenac	261	261	.	253
12252	declofenac	11	11	11	11
12815	declofenac	7	7	7	7
10579	Ibuprofen	13	18	.	13
11377	Ibuprofen	4	4	.	4
11767	Ibuprofen	123	123	.	123
21191	Ibuprofen	13	13	.	17
12446	Ibuprofen	9	9	9	5
11011	Ibuprofen	112	.	.	124

* :Time to Mild-Moderate-Severe GI AE
** :Time to Moderate-Severe GI AE
*** :Time to Severe GI AE
****:Time to CSUGIE

Table 10. CSUGIE Incidence in GI AE Groups and Non-GI AE Groups

	Celebrex	Declofenac	Ibupfrofen	Overall
With MD-MT-SEV GI AE	2/1383 (0.14%)	1/857 (0.12%)	2/639 (0.31%)	5/2879 (0.17%)
Without MD-MT-SEV GI AE	15/2604 (0.58%)	9/1139 (0.79%)	9/1346 (0.67%)	33/5089 (0.65%)
Relative Risk	25.10%	14.77%	46.81%	26.78%
With MT-SEV GI AE	0/694 (0.00%)	1/441 (0.23%)	1/332 (0.30%)	2/1467 (0.14%)
Without MT-SEV GI AE	17/3293 (0.52%)	9/1555 (0.58%)	10/1653 (0.60%)	36/6501 (0.55%)
Relative Risk	0.00%	39.18%	49.79%	24.62%
With SEV GI AE	0/154 (0.00%)	0/125 (0.00%)	0/71 (0.00%)	0/350 (0.00%)
Without SEV GI AE	17/3833 (0.44%)	10/1871 (0.53%)	11/1914 (0.57%)	38/7618 (0.50%)
Relative Risk	0.00%	0.00%	0.00%	0.00%

IV. 2 Analysis for the First 6 Months Data

The sponsor's rationale for analyzing the first 6 months data only is that the large dropout rate in the later stage of the study depleted high-risk patients--patients who dropped out due to GI AEs. This rationale is not valid due to the following reasons.

1) Current statistical methods in survival analysis (K-M estimator, tests for time to events) can make valid statistical inference even with high proportion of censoring, unless the censoring is informative. Sponsor's argument for the existence of informative censoring was not supported by the data as discussed in Comment 1 above. Therefore, this reviewer regards the analysis for data for the entire study period as specified in the protocol, which includes most information, the appropriate analysis.

2) The 6 months analysis is not valid even with concern of informative censoring. As presented in Table 11, the drop-out rates due to GI AE were increased gradually without sudden increase at Month 6 (Week 26) in any of the treatment groups. The numerical order of the drop-out rates stayed the same across the entire study period. Therefore, there is no reason to include information only in the first 6 months.

Table 11. Drop-out Rates (%) due to GI AE

TimePoint	Celebrex (n=3987)	Diclofenac (n=1996)	Ibuprofen (n=1985)
Week1	2.85	4.25	2.80
Week4	5.08	7.46	5.09
Week13	8.20	11.05	8.94
Week26	9.90	13.66	10.54
Week39	11.09	14.65	11.59
Week52	11.41	14.95	11.71
Week65	11.41	14.95	11.99

IV.3 Subgroup Analysis for Non-Aspirin Users

As presented in Table 6 and Table 7, the sponsor conducted analysis for CSUGIE and combined CSUGIE/GDU event rates in non-aspirin users. The sponsor's analyses showed that celebrex had a numerically lower CSUGIE/GDU incidence (0.3%) than in ibuprofen group (0.6%) with a p-value 0.185 and a numerically lower CSUGIE/GDU incidence (0.7%) than in ibuprofen group (1.8%) with a p-value less than 0.05. These p-values can not be interpreted by their face values since 1) the primary endpoint did not show statistical significance, 2) numerous subgroup analyses had been conducted (at least 34, see Tables a9-a11 in Appendix A for the results of risk factor analyses) in exploratory faction with no pre-specified plan of statistical inference, and 3) subgroup analyses based on aspirin use was not even mentioned in the protocol. However, if these subgroup analyses are clinically meaningful and the results are supported by external information (see DR. Goldkind's review for further comments), the conventional frequentist's approach of adjusting α may not be appropriate. But a formal statistical inference is impossible without a pre-specified analysis plan.

It is also worth noticing that the results of CSUGIE and combined CSUGIE/GDU event rates in aspirin users were numerically inconsistent with that in the non-user group—celebrex had higher incidences (1.0% for CSUGIE and 2.5% for combined CSUGIE/GDU event) than ibuprofen group (0.2% for CSUGIE and 1.9% for combined CSUGIE/GDU event) (see Tables a11 and a12 in Appendix A).

V. Final Conclusion

Celebrex 400 mg BID did not show significant reduction in CSUGIE incidence compared to two NSAIDs: ibuprofen 800 mg TID and diclofenac 75 mg BID in patients with OA or RA.

In a post hoc analysis of non-aspirin users, the incidence of combined CSUGIE/GDU event in the celebrex group was lower than that in ibuprofen group with p-values less than 0.05. However, this p-value can not be easily interpreted statistically by its face value due to lack of

pre-specified analysis plan and the failure of showing statistical significance in the primary endpoint.

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NDA 20998
HFD-550/MO/Goldkind/Witter/Bullj
HFD-550/PM/Kongy
HFD-550/Div. File
HFD-725/Lu/Lin ST./Huque
HFD-725/Div. File

Appendix A

Table a1. Baseline Demographics

	Celecoxib 400 mg BID (N=3987)	Diclofenac 75 mg BID (N=1996)	Ibuprofen 800 mg TID (N=1985)
AGE (yrs)			
N	3987	1996	1985
Mean	60.6	60.1	59.5
SD	11.66	11.99	11.93
Median	61.0	61.0	60.0
Range	20- 89	21- 90	18- 90
<= 34	76 (1.9%)	52 (2.6%)	49 (2.5%)
35 - 44	272 (6.8%)	166 (8.3%)	172 (8.7%)
45 - 54	881 (22.1%)	404 (20.2%)	458 (23.1%)
55 - 64	1199 (30.1%)	612 (30.7%)	582 (29.3%)
65 - 74	1072 (26.9%)	526 (26.4%)	507 (25.5%)
>= 75	487 (12.2%)	236 (11.8%)	217 (10.9%)
GENDER			
Male	1255 (31.5%)	650 (32.6%)	580 (29.2%)
Female	2732 (68.5%)	1346 (67.4%)	1405 (70.8%)
TOTAL	3987 (100.0%)	1996 (100.0%)	1985 (100.0%)
RACE/ETHNIC ORIGIN			
Caucasian	3528 (88.5%)	1784 (89.4%)	1713 (86.3%)
Black	301 (7.5%)	151 (7.6%)	172 (8.7%)
Asian	29 (0.7%)	19 (1.0%)	9 (0.5%)
Hispanic	107 (2.7%)	36 (1.8%)	75 (3.8%)
Other	22 (0.6%)	6 (0.3%)	16 (0.8%)
TOTAL	3987 (100.0%)	1996 (100.0%)	1985 (100.0%)

Table a2. Additional Baseline Characters

	Celecoxib 400 mg BID (N=3987)	Diclofenac 75 mg BID (N=1996)	Ibuprofen 800 mg TID (N=1985)
HEIGHT (cm)			
N	3969	1984	1971
Mean	166.73	167.01	166.53
SD	9.999	10.171	10.042
Median	165.10	165.10	165.10
Range	118.8-203.2	106.2-203.2	135.0-210.8
WEIGHT (kg)			
N	3961	1989	1973
Mean	84.11	83.74	84.57
SD	21.227	20.663	21.212
Median	81.40	81.20	80.90
Range	36.5-204.5	40.8-190.9	36.3-179.5

Table a3. Vital Signs

	Celecoxib 400 mg BID (N=3987)	Diclofenac 75 mg BID (N=1996)	Ibuprofen 800 mg TID (N=1985)
TEMPERATURE (C)			
N	3937	1962	1969
Mean	36.61	36.61	36.61
SD	0.436	0.436	0.407
Median	36.70	36.60	36.70
Range	32.8- 40.9	34.6- 40.2	32.9- 38.1
SITTING PULSE (beats/min)			
N	3976	1989	1982
Mean	73.8	74.1	73.6
SD	9.62	9.22	9.68
Median	73.0	72.0	72.0
Range	46-120	44-126	46-120
SITTING RESPIRATION (breaths/min)			
N	3969	1984	1978
Mean	17.0	17.1	17.0
SD	2.85	3.07	2.73
Median	16.0	16.0	16.0
Range	8- 40	8- 36	8- 36
SITTING SYSTOLIC BLOOD PRESSURE (mm Hg)			
N	3980	1989	1983
Mean	132.7	133.0	132.6
SD	17.03	17.14	16.68
Median	130.0	132.0	130.0
Range	80-200	84-238	90-202
SITTING DIASTOLIC BLOOD PRESSURE (mm Hg)			
N	3980	1989	1983
Mean	79.4	79.5	79.9
SD	9.28	9.31	9.12
Median	80.0	80.0	80.0
Range	38-120	48-130	50-118

Table a4. GI Risk Factors

HISTORY OF:	Celecoxib 400 mg BID (N=3987)	Diclofenac 75 mg BID (N=1996)	Ibuprofen 800 mg TID (N=1985)
UPPER GI BLEEDING			
Yes	68 (1.7%)	30 (1.5%)	28 (1.4%)
No	3919 (98.3%)	1966 (98.5%)	1957 (98.6%)
TOTAL	3987 (100.0%)	1996 (100.0%)	1985 (100.0%)
GASTRODUODENAL ULCER			
Yes	334 (8.4%)	170 (8.5%)	151 (7.6%)
No	3653 (91.6%)	1826 (91.5%)	1834 (92.4%)
TOTAL	3987 (100.0%)	1996 (100.0%)	1985 (100.0%)
GI-RELATED NSAID INTOLERANCE (b)			
Yes	347 (8.7%)	202 (10.1%)	165 (8.3%)
No	3640 (91.3%)	1794 (89.9%)	1820 (91.7%)
TOTAL	3987 (100.0%)	1996 (100.0%)	1985 (100.0%)
CARDIOVASCULAR DISEASE			
Yes	1602 (40.2%)	805 (40.3%)	794 (40.0%)
No	2384 (59.8%)	1190 (59.6%)	1190 (59.9%)
TOTAL	3986 (100.0%)	1995 (99.9%)	1984 (99.9%)
FLEXSURE FOR H. PYLORI			
Negative	2448 (61.4%)	1243 (62.3%)	1213 (61.1%)
Positive	1536 (38.5%)	752 (37.7%)	769 (38.7%)
TOTAL	3984 (99.9%)	1995 (99.9%)	1982 (99.8%)

Table a4. GI Risk Factors (continue)

HISTORY OF:	Celecoxib 400 mg BID (N=3987)	Diclofenac 75 mg BID (N=1996)	Ibuprofen 800 mg TID (N=1985)
ALCOHOL USE			
None	2753 (69.0%)	1184 (59.3%)	1599 (80.6%)
Yes (b)	1232 (30.9%)	812 (40.7%)	386 (19.4%)
1 or Fewer Drinks per Day	1079 (27.1%)	712 (35.7%)	326 (16.4%)
2-3 Drinks per Day	130 (3.3%)	93 (4.7%)	46 (2.3%)
4 or More Drinks per Day	11 (0.3%)	7 (0.4%)	2 (0.1%)
Yes - No Specification	12 (0.3%)	0 (0.0%)	12 (0.6%)
TOTAL	3985 (99.9%)	1996 (100.0%)	1985 (100.0%)
TOBACCO USE (c)			
None	3356 (84.2%)	1685 (84.4%)	1701 (85.7%)
Yes (b)	629 (15.8%)	311 (15.6%)	284 (14.3%)
Level I	198 (5.0%)	100 (5.0%)	62 (3.1%)
Level II	229 (5.7%)	152 (7.6%)	75 (3.8%)
Level III	85 (2.1%)	59 (3.0%)	30 (1.5%)
Yes - No Specification	116 (2.9%)	0 (0.0%)	117 (5.9%)
TOTAL	3985 (99.9%)	1996 (100.0%)	1985 (100.0%)
CORTICOSTEROID USE			
None	2768 (69.4%)	1428 (71.5%)	1378 (69.4%)
One Dose to <10% Study Days	413 (10.4%)	183 (9.2%)	214 (10.8%)
>=10% Study Days	806 (20.2%)	385 (19.3%)	393 (19.8%)
TOTAL	3987 (100.0%)	1996 (100.0%)	1985 (100.0%)
ANTICOAGULANT USE			
None	3945 (98.9%)	1972 (98.8%)	1965 (99.0%)
One Dose to <10% Study Days	24 (0.6%)	8 (0.4%)	8 (0.4%)
>=10% Study Days	18 (0.5%)	16 (0.8%)	12 (0.6%)
TOTAL	3987 (100.0%)	1996 (100.0%)	1985 (100.0%)
ASPIRIN USE			
None	3105 (77.9%)	1551 (77.7%)	1573 (79.2%)
One Dose to <10% Study Days	196 (4.9%)	104 (5.2%)	83 (4.2%)
>=10% Study Days	686 (17.2%)	341 (17.1%)	329 (16.6%)
TOTAL	3987 (100.0%)	1996 (100.0%)	1985 (100.0%)
ASPIRIN USE DURING FIRST SIX MONTHS			
None	3154 (79.1%)	1567 (78.5%)	1602 (80.7%)
Any	833 (20.9%)	429 (21.5%)	383 (19.3%)
TOTAL	3987 (100.0%)	1996 (100.0%)	1985 (100.0%)

Table a5. Summary of Patient's Global Assessment Results

	Celebrex 400 mg BID (n=3987)	Diclofenac 75 mg BID (n=1996)	Ibuprofen 800 mg TID (n=1985)
Mean (95% CI)*			
Baseline	2.96 (2.93-2.98)	2.95 (2.91-2.99)	2.96 (2.92-3.00)
Week 26	2.68 (2.65-2.71)	2.71 (2.67-2.76)	2.73 (2.68-2.78)
Final	2.71 (2.68-2.74)	2.72 (2.67-2.77)	2.76 (2.71-2.81)
Categorical analysis, % (95% CI)			
Week 26			
Improved	38 (37-40)	40 (38-42)	32 (30-34)
No Change	46 (45-48)	43 (41-45)	48 (46-50)
Worsened	16 (15-17)	17 (15-18)	20 (18-21)
Final			
Improved	37 (35-38)	40 (38-43)	31 (29-33)
No Change	46 (44-47)	42 (40-44)	48 (46-50)
Worsened	18 (16-19)	18 (16-19)	21 (19-23)

Table a6. Summary of Patient's Assessment of Arthritis Pain (VAS) Results

	Celebrex 400 mg BID (n=3987)	Diclofenac 75 mg BID (n=1996)	Ibuprofen 800 mg TID (n=1985)
Mean (95% CI)			
Baseline	50.7 (49.9-51.6)	50.8 (49.6-52.1)	50.6 (49.3-51.9)
Week 26	42.9 (42.0-43.7)	43.4 (42.0-44.8)	45.0 (43.6-46.4)
Final	44.0 (43.1-44.9)	44.2 (42.7-45.6)	45.9 (44.5-47.4)

Table a7. Incidence of Withdrawal Due to Lack of Arthritis Efficacy

	Celebrex 400 mg BID (n=3987)	Diclofenac 75 mg BID (n=1996)	Ibuprofen 800 mg TID (n=1985)
Number (Percent) (95% Confidence Interval)	691(17%) (16% - 19%)	309(15%) (14% - 17%)	456(23%) (21% - 25%)

Table a8. Summary of Results in Selected SF-36 Health Survey Domains

SF-36 Health Survey Domain	Celebrex 400 mg BID (n=1990)	Ibuprofen 800 mg TID (n=1985)
Bodily Pain		
Baseline	39.5 (38.6-40.4)	39.9 (39.0-40.8)
Week 26	46.0 (45.1-46.9)	44.8 (43.9-45.8)
Final	45.9 (45.0-46.9)	44.7 (43.8-45.7)
Physical Function		
Baseline	48.3 (47.1-49.5)	48.6 (47.4-49.9)
Week 26	51.4 (50.5-52.3)	50.4 (49.4-51.3)
Final	50.8 (49.9-51.7)	50.1 (49.2-51.0)
Vitality		
Baseline	45.4 (44.3-46.4)	46.1 (45.0-47.1)
Week 26	47.6 (46.7-48.4)	46.9 (46.0-47.7)
Final	47.0 (46.1-47.8)	46.3 (45.5-47.1)
Role-Physical		
Baseline	37.9 (35.9-39.8)	38.4 (36.4-40.3)
Week 26	42.6 (40.8-44.4)	41.0 (39.2-42.8)
Final	42.1 (40.4-43.9)	41.0 (39.2-42.8)

Table a9. Risk Factor Analysis of Clinically Significant UGI Events (Demographics)

	Celecoxib 400 mg BID (N = 3987)	Diclofenac 75 mg BID (N = 1996)	Ibuprofen 800 mg TID (N = 1985)	P-Value (a) Treatment by Factor Interaction	P-Value (a) Factor Effect
AGE (years)					
<75	10/3580 (0.3%)	9/1768 (0.5%)	7/1768 (0.4%)	0.837	<0.001
>=75	7/ 489 (1.4%)	5/ 236 (2.1%)	4/ 217 (1.8%)		
P-VALUE(b)	<0.001	<0.001	0.007		
GENDER					
MALE	6/1255 (0.5%)	4/ 650 (0.6%)	4/ 580 (0.7%)	0.475	0.170
FEMALE	11/2732 (0.4%)	4/1346 (0.3%)	7/1405 (0.5%)		
P-VALUE(b)	0.768	0.082	0.625		
DISEASE TYPE					
OA	14/2898 (0.5%)	8/1453 (0.6%)	8/1434 (0.6%)	0.855	0.312
RA	3/1089 (0.3%)	2/ 543 (0.4%)	3/ 551 (0.5%)		
P-VALUE(b)	0.341	0.597	0.928		
DURATION (OA)					
< 5 YEARS	3/ 965 (0.3%)	3/ 484 (0.6%)	6/ 497 (1.2%)	0.052	0.519
>= 5 YEARS	11/1918 (0.6%)	5/ 963 (0.5%)	2/ 927 (0.2%)		
P-VALUE(b)	0.327	0.816	0.038		
DURATION (RA)					
< 5 YEARS	2/ 333 (0.6%)	0/ 181 (0.0%)	0/ 168 (0.0%)	0.063	0.640
>= 5 YEARS	1/ 738 (0.1%)	2/ 345 (0.6%)	3/ 374 (0.8%)		
P-VALUE(b)	0.229	0.952	0.994		
PATIENT'S GLOBAL ASSESSMENT AT BASELINE					
POOR OR VERY POOR	6/ 713 (0.8%)	5/ 362 (1.4%)	2/ 335 (0.6%)	0.352	0.007
OTHER	11/3274 (0.3%)	5/1634 (0.3%)	9/1650 (0.5%)		
P-VALUE(b)	0.037	0.013	0.018		

Table a10. Risk Factor Analysis of Clinically Significant UGI Events (GI History)

	Celecoxib 400 mg BID (N = 3987)	Diclofenac 75 mg BID (N = 3956)	Ibuprofen 800 mg TID (N = 3985)	P-Value (a) Treatment by Factor Interaction	P-Value (a) Factor Effect
HISTORY OF UPPER GI BLEEDING					
YES	1/ 68(1.5%)	0/ 30(0.0%)	2/ 23(7.1%)	0.207	0.017
NO	16/3919(0.4%)	10/1964(0.5%)	9/1957(0.5%)		
P-VALUE(b)	0.144	0.994	<0.001		
HISTORY OF GASTRODUODENAL ULCER					
YES	2/ 334(0.6%)	4/ 170(2.4%)	1/ 151(0.7%)	0.189	0.030
NO	15/3653(0.4%)	6/1826(0.3%)	10/1834(0.5%)		
P-VALUE(b)	0.669	0.002	0.762		
HISTORY OF UPPER GI BLEEDING OR GASTRODUODENAL ULCER					
YES	2/ 353(0.6%)	4/ 184(2.2%)	3/ 162(1.2%)	0.263	0.022
NO	15/3634(0.4%)	6/1816(0.3%)	9/1823(0.5%)		
P-VALUE(b)	0.554	0.003	0.183		
HISTORY OF GI-RELATED BRAIN INTOLERANCE					
YES	1/ 347(0.3%)	2/ 202(1.0%)	2/ 165(1.2%)	0.993	0.055
NO	14/3640(0.4%)	8/1794(0.4%)	9/1820(0.5%)		
P-VALUE(b)	0.193	0.272	0.222		
HISTORY OF CARDIOVASCULAR DISEASE					
YES	14/1602(0.9%)	7/ 885(0.8%)	4/ 784(0.5%)	0.036	<0.001
NO	3/2384(0.1%)	3/1150(0.3%)	7/1190(0.6%)		
P-VALUE(b)	0.002	0.064	0.793		
PRESENCE FOR H. PYLORI					
POSITIVE	5/1536(0.3%)	5/ 752(0.7%)	7/ 769(0.9%)	0.170	0.305
NEGATIVE	12/2458(0.5%)	5/1263(0.4%)	4/1213(0.3%)		
P-VALUE(b)	0.460	0.417	0.092		

Table a11. Risk Factor Analysis of Clinically Significant UGI Events (Medication, Alcohol, and Tobacco Use)

	Celecoxib 400 mg BID (N = 3987)	Diclofenac 75 mg BID (N = 3956)	Ibuprofen 800 mg TID (N = 3985)	P-Value (a) Treatment by Factor Interaction	P-Value (a) Factor Effect
CORTICOSTEROID USE					
ANY	3/1219(0.2%)	2/ 568(0.4%)	2/ 607(0.3%)	0.954	0.949
NONE	14/2768(0.5%)	8/1438(0.6%)	9/1378(0.7%)		
P-VALUE(b)	0.171	0.583	0.276		
ASPIRIN USE					
ANY	9/ 882(1.0%)	6/ 445(1.3%)	1/ 412(0.2%)	0.920	0.006
NONE	8/3105(0.3%)	4/1951(0.2%)	10/1573(0.6%)		
P-VALUE(b)	0.005	0.010	0.355		
ALCOHOL USE					
ANY	4/1232(0.3%)	5/ 612(0.8%)	4/ 386(1.0%)	0.326	0.605
NONE	13/2753(0.5%)	5/1184(0.4%)	7/1595(0.4%)		
P-VALUE(b)	0.586	0.574	0.166		
TOBACCO USE					
ANY	0/ 628(0.0%)	2/ 311(0.6%)	0/ 284(0.0%)	0.067	0.059
NONE	17/3356(0.5%)	8/1685(0.5%)	11/1701(0.6%)		
P-VALUE(b)	0.883	0.657	0.992		
ANTICOAGULANT USE					
ANY	0/ 42(0.0%)	0/ 24(0.0%)	0/ 20(0.0%)	1.000	0.339
NONE	17/3945(0.4%)	10/1972(0.5%)	11/1965(0.6%)		
P-VALUE(b)	0.993	0.994	0.992		

Table a12. Risk Factor Analysis of Clinically Significant UGI Events or GD Ulcer (Medication, Alcohol, and Tobacco Use)

	Celecoxib 400 mg BID (N = 3987)	Diclofenac 75 mg BID (N = 1996)	Ibuprofen 800 mg TID (N = 1985)	P-Value (a) Treatment by Factor Interaction	P-Value (a) Factor Effect
CORTICOSTEROID USE					
ANY	10/1219 [0.8%]	6/ 568 [1.1%]	12/ 607 [2.0%]	0.707	0.123
NONE	33/2768 [1.2%]	20/1428 [1.4%]	25/1378 [1.7%]		
P-VALUE (b)	0.150	0.397	0.776		
ASPIRIN USE					
ANY	22/ 482 [2.5%]	16/ 445 [3.6%]	8/ 412 [1.9%]	0.004	<0.001
NONE	21/3105 [0.7%]	10/1551 [0.6%]	28/1573 [1.8%]		
P-VALUE (b)	<0.001	<0.001	0.960		
ALCOHOL USE					
ANY	10/1232 [0.8%]	15/ 812 [1.8%]	5/ 386 [1.3%]	0.112	0.934
NONE	33/2753 [1.2%]	11/1183 [0.9%]	31/1599 [1.9%]		
P-VALUE (b)	0.351	0.099	0.463		
TOBACCO USE					
ANY	2/ 628 [0.3%]	5/ 313 [1.6%]	2/ 284 [0.7%]	0.106	0.054
NONE	41/3356 [1.2%]	21/1685 [1.2%]	34/1701 [2.0%]		
P-VALUE (b)	0.074	0.588	0.146		
ANTICOAGULANT USE					
ANY	1/ 42 [2.4%]	0/ 24 [0.0%]	0/ 20 [0.0%]	0.382	0.821
NONE	42/3945 [1.1%]	26/1972 [1.3%]	36/1965 [1.8%]		
P-VALUE (b)	0.453	0.994	0.994		

Appendix B

Discussions On Informative Censoring And Risk Factor-Related Withdrawal

In design and analysis of failure data with censoring, an important requirement is that dropouts are non-informative, that is, the failure time is independent of the reason for the individual to drop out before the event is possibly observed. However, this assumption cannot be met if the failure time is censored through withdrawal as a result of a deterioration of patient condition. This type of censoring is known as informative censoring, a special type of non-ignorable missing data. When present, informative censoring causes bias in standard analyses, and interpretation of such analyses may be misleading. In this section, we discuss the informative censoring in the present study caused by withdrawal due to GI-related symptoms, and the statistical analysis and simulation adjusted for the informative censoring. We also present the withdrawal vs. GI risk factors over time and its impact on the analysis.

Informative Censoring Caused by Withdrawal due to GI-Related Symptoms

In this study, informative censoring with respect to study end points, namely clinically significant UGI events (CSUGIEs) and CSUGIEs combined with gastroduodenal ulcers (CSUGIEs/GDUs), was observed in patients who dropped out due to GI-related adverse events, including dyspepsia, abdominal pain, nausea, diarrhea, and vomiting. First, a treatment differentiation in time to and incidence of dropout due to GI adverse events was detected. Second, the rates of CSUGIEs were different in patients without GI adverse events than in patients with GI adverse events. Patients who experienced GI adverse events had a higher incidence of CSUGIEs than patients who did not report GI adverse events. Clearly, a patient whose failure time is censored due to a GI adverse event causing withdrawal represents a higher risk for an event than those who have not had an adverse event up to that time.

Table 1. Summary of Abdominal Pain, Dyspepsia, Nausea, Diarrhea and Vomiting Incidence and Withdrawals (Moderate to Severe)

	Celecoxib n (%)	Diclofenac n (%)	Ibuprofen n (%)
Treated	3987	1996	1985
Any GI AE	699	448	336
Withdrawal	298 (7.5)	191 (9.6)	149 (7.5)

Similar summaries including mild, moderate, and severe GI adverse events and withdrawals are included in Appendix 2.4.17. Significantly higher withdrawal incidence and earlier withdrawal time in the diclofenac group were detected than in the other treatment groups ($p<0.01$). To assess whether the withdrawals due to GI-related adverse events affected the estimation of clinically significant UGI event rates, we examined the relative risks of CSUGIEs and CSUGIEs/GDUs in patients with and without GI symptoms.

Table 2. Summary of CSUGIE Rates and Relative Risks With and Without Five GI Adverse Events (Moderate to Severe)

	Celecoxib	Diclofenac	Ibuprofen
CSUGIEs			
With AE	5/699	8/448	5/336
Without AE	12/3288	2/1548	6/1649
Relative risk	1.96	13.82	4.09
CSUGIEs / GDUs			
With AE	22/699	20/448	20/336
Without AE	21/3288	6/1548	16/1649
Relative risk	4.93	11.52	6.13

The table indicates that the patients with GI adverse events would have higher probability to develop an event over the treatment duration. A high and early withdrawal rate due to GI-related adverse events diminished the real event rate of the patient population. A bias would have been created in favor of treatments with high withdrawal rates due to shorter exposure time to treatment, hence lower event rates. Therefore, an estimation for the entire study period without adjustment for informative dropouts would not be appropriate for interpretation.

VI. Statistical Adjustment for Informative Censoring

Informative censoring has been widely discussed in many statistical journals over the past 20 years. There have been some proposals under certain assumptions dealing with continuous data and some other specific types of data when dropouts do not occur at random. For references, reviewers should refer to D. Rubin (1976, Biometrika, vol. 63, pp. 581-592), P. Diggle and M. Kenward (1994, Appl. Statist., Vol. 43, pp. 49-93), and J. Little (1995, JASA, vol. 90, pp. 1112-1121).

In this study, informative censoring occurred, and our primary end point is survival-type data. We will analyze the data by estimating the events missed due to informative withdrawal-based dropout incidences and times. A total probability will be calculated and simulation will be performed for Kaplan-Meier curves adjusted for the withdrawal. Fisher's exact test will be performed on the adjusted event rates.

As seen in prior discussions, treatment differentiation withdrawals due to GI adverse events and higher relative risks in the patients with GI adverse events were observed. Intuitively, early withdrawal of patients due to GI adverse events would have introduced underestimates of overall CSUGIE and ulcer rates because the probability for a patient to develop a UGI event or ulcer is higher if the patient has a GI adverse event or discontinues due to a GI adverse event. Therefore, the overall CSUGIE or ulcer rate, or the total probability of developing a CSUGIE or ulcer for the treated patient population, should be estimated by partitioning the samples into three subsets.

Prob. (event occurred) = P (event | no GI AE) * P (no GI AE)
+ P (event | GI AE and continue) * P (GI AE and continue)
+ P (event | GI AE and withdrawal) * P (GI AE and withdrawal)

The first and second terms shall be estimated by the corresponding sample means, respectively. The third term represents the missing event rate due GI adverse event-related withdrawal. To estimate the number of CSUGIEs we would have observed had the patients not dropped out due to adverse events, we calculated the total exposure time after the GI adverse events were reported for the patients with adverse events who did not drop out as a result. The total number of the events occurring in these continuing patients with adverse events divided by this exposure would give us the estimated rate by patient exposure time after the adverse event was reported. We assume the rate in the patients who discontinued due to GI adverse events over the period between the adverse event and the end of the treatment would have been at least as high had the patients continued treatment as the rate in those who continued. The exposure times for the patients who withdrew due to adverse events were estimated by calculating the time between the dropout date and the end of the study. For the entire study period, the date of 1/10/2000 was used as the end of the study. This date is one month after the official letter of closing the study was issued, and is five days after the last withdrawal due to a GI adverse event. For the analyses of the first six months, the dates of 7/10/2000 and 9/10/2000 were used for protocols 035 and 102, respectively, due to the lag in enrollment time of 102 by approximately two months.

Table 3 summarizes the adjusted event rates and statistical tests applied. Detailed data can be found in Appendices 2.4.17.9 – 2.4.17.14.

Table 3. CSUGIE and Ulcer Rates Adjusted for Discontinuation due to Moderate and Severe GI Adverse Events

				p-values		
	Celecoxib	**Diclofenac**	**Ibuprofen**	**C/N**	**C/D**	**C/I**
Patients	3984	1995	1983			
First 6 Month						
CSUGIE	15	16	16	.013	.036	.035
CSUGIE/GDU	44	34	44	.002	.069	.001
Entire period						
POB	25	23	21	.022	.044	.084
PUB	76	58	73	<.01	.016	<.01

With the above rates, we simulated Kaplan-Meier curves for the three treatment groups. In each run, the estimated events were randomly assigned to the patients who discontinued due to GI adverse events. The simulations were performed 100 times; the averaged curve is presented below.

EXHIBIT 13

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-998/S-009

G.D. Searle
Attention: Eva Essig, Ph.D.
Associate Director, Worldwide Regulatory Affairs
4901 Searle Parkway
Skokie, Illinois 60077

Dear Dr. Essig:

Please refer to your supplemental new drug application dated June 12, 2000, received June 14, 2000, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Celebrex (celecoxib capsules) Capsules, 100 mg and 200 mg.

We acknowledge receipt of your submissions dated June 21; July 12 and 17; September 29; October 11 and 20; November 3, 17, 21, 22 and 30; December 14 (two), 15 (two) and 21, 2000; January 5 (three), 10, 22 (two), 23, 24 and 31; February 1 (two), 2, 14 and 27; March 15 and 26; and April 4 (two), 2001.

This supplemental new drug application provides for changes to the **Warnings** and **Clinical Studies** sections of the labeling based on a large gastrointestinal outcome study for Celebrex.

We have completed the review of this application, as amended, and it is approvable. Before this application may be approved, however, it will be necessary for you to submit revised draft labeling for the drug as indicated in the enclosed/marked-up draft.

In addition, all previous revisions as reflected in the most recently approved labeling must be included. To facilitate review of your submission, please provide a highlighted or marked-up copy that shows the changes that are being made.

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

Under 21 CFR 314.50(d)(5)(vi)(*b*), we request that you update your NDA by submitting all safety information you now have regarding your new drug. The safety update should include data from all nonclinical and clinical studies of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.

2. When assembling the sections describing discontinuations due to adverse events, serious

adverse events, and common adverse events, incorporate new safety data as follows:

- Present new safety data from the studies for the proposed indication using the same format as the original NDA submission.
- Present tabulations of the new safety data combined with the original NDA data.
- Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.
- For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.

3. Present a retabulation of the reasons for premature study discontinuation by incorporating the drop-outs from the newly completed studies. Describe any new trends or patterns identified.

4. Provide case report forms and narrative summaries for each patient who died during a clinical study or who did not complete a study because of an adverse event. In addition, provide narrative summaries for serious adverse events.

5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.

6. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.

7. Provide English translations of current approved foreign labeling not previously submitted.

In addition, please submit three copies of the introductory promotional materials that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to this Division and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Within 10 days after the date of this letter, you are required to amend the supplemental application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of any such action FDA may proceed to withdraw the application. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

Under 21 CFR 314.102(d) of the new drug regulations, you may request an informal meeting or telephone conference with this division to discuss what further steps need to be taken before the application may be approved.

This product may be considered to be misbranded under the Federal Food, Drug, and Cosmetic Act if it is marketed with these changes prior to approval of this supplemental application.

If you have any questions, call Yoon J. Kong, Pharm.D., Regulatory Project Manager, at (301) 827-2090.

Sincerely,

{See appended electronic signature page}

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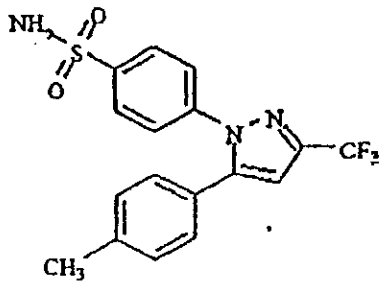
Enclosure

WORKING COPY OF LABEL - CLASS
CELEBREX®
(celecoxib capsules)

DESCRIPTION

CELEBREX (celecoxib) is chemically designated as 4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl] benzenesulfonamide and is a diaryl substituted pyrazole. It has the following chemical structure:



The empirical formula for celecoxib is $C_{17}H_{14}F_3N_3O_2S$, and the molecular weight is 381.38.

CELEBREX oral capsules contain 100 mg and 200 mg of celecoxib.

The inactive ingredients in CELEBREX capsules include: croscarmellose sodium, edible inks, gelatin, lactose monohydrate, magnesium stearate, povidone, sodium lauryl sulfate and titanium dioxide.

CLINICAL PHARMACOLOGY

Mechanism of Action: Celebrex is a nonsteroidal anti-inflammatory drug that exhibits anti-inflammatory, analgesic, and antipyretic activities in animal models. The mechanism of action of CELEBREX is believed to be due to inhibition of prostaglandin synthesis, primarily via inhibition of cyclooxygenase-2 (COX-2), and at therapeutic concentrations in humans, CELEBREX does not inhibit the cyclooxygenase-1 (COX-1) isoenzyme. In animal colon tumor models, celecoxib reduced the incidence and multiplicity of tumors.

Pharmacokinetics:

Absorption

Peak plasma levels of celecoxib occur approximately 3 hrs after an oral dose. Under fasting conditions, both peak plasma levels (Cmax) and area under the curve (AUC) are roughly dose proportional up to 200 mg BID; at higher doses there are less than proportional increases in Cmax and AUC (see Food Effects). Absolute bioavailability studies have not been conducted. With multiple dosing, steady state conditions are reached on or before day 5.

The pharmacokinetic parameters of celecoxib in a group of healthy subjects are shown in Table 1.

Table 1: Summary of Single Dose (200 mg) Disposition Kinetics of Celecoxib in Healthy Subjects[1]

Mean (%CV) PK Parameter Values				
Cmax, ng/mL	Tmax, hr	Effective t1/2, hr	Vss/F, L	CL/F, L/hr
705 (38)	2.8 (37)	11.2 (31)	429 (34)	27.7 (28)

[1] Subjects under fasting conditions (n=36, 19-52 yrs.)

Food Effects
When CELEBREX capsules were taken with a high fat meal, peak plasma levels were delayed for about 1 to 2 hours with an increase in total absorption (AUC) of 10% to 20%. Under fasting conditions, at doses above 200 mg, there is less than a proportional increase in C_{max} and AUC, which is thought to be due to the low solubility of the drug in aqueous media. Coadministration of CELEBREX with an aluminum- and magnesium-containing antacid resulted in a reduction in plasma celecoxib concentrations with a decrease of 37% in Cmax and 10% in AUC. CELEBREX, at doses up to 200 mg BID can be administered without regard to timing of meals. Higher doses (400 mg BID) should be administered with food to improve absorption.

Distribution
In healthy subjects, celecoxib is highly protein bound (~97%) within the clinical dose range. *In vitro* studies indicate that celecoxib binds primarily to albumin and, to a lesser extent, α_1-acid glycoprotein. The apparent volume of distribution at steady state (V_{ss}/F) is approximately 400 L, suggesting extensive distribution into the tissues. Celecoxib is not preferentially bound to red blood cells.

Metabolism
Celecoxib metabolism is primarily mediated via cytochrome P450 2C9. Three metabolites, a primary alcohol, the corresponding carboxylic acid and its glucuronide conjugate, have been identified in human plasma. These metabolites are inactive as COX-1 or COX-2 inhibitors. Patients who are known or suspected to be P450 2C9 poor metabolizers based on a previous history should be administered celecoxib with caution as they may have abnormally high plasma levels due to reduced metabolic clearance.

Excretion
Celecoxib is eliminated predominantly by hepatic metabolism with little (<3%) unchanged drug recovered in the urine and feces. Following a single oral dose of radiolabeled drug, approximately 57% of the dose was excreted in the feces and 27% was excreted into the urine. The primary metabolite in both urine and feces was the carboxylic acid metabolite (73% of dose) with low amounts of the glucuronide also appearing in the urine. It appears that the low solubility of the drug prolongs the absorption process making terminal half-life ($t_{1/2}$) determinations more variable. The effective half-life is approximately 11 hours under fasted conditions. The apparent plasma clearance (CL/F) is about 500 mL/min.

Special Populations

Geriatric: At steady state, elderly subjects (over 65 years old) had a 40% higher Cmax and a 50% higher AUC compared to the young subjects. In elderly females, celecoxib Cmax and AUC are higher than those for elderly males, but these increases are predominantly due to lower body weight in elderly females. Dose adjustment in the elderly is not generally necessary. However, for patients of less than 50 kg in body weight, initiate therapy at the lowest recommended dose.

Pediatric: CELEBREX capsules have not been investigated in pediatric patients below 18 years of age.

Race: Meta-analysis of pharmacokinetic studies has suggested an approximately 40% higher AUC of celecoxib in Blacks compared to Caucasians. The cause and clinical significance of this finding is unknown.

Hepatic Insufficiency: A pharmacokinetic study in subjects with mild (Child-Pugh Class I) and moderate (Child-Pugh Class II) hepatic impairment has shown that steady-state celecoxib AUC is increased about 40% and 180%, respectively, above that seen in healthy control subjects. Therefore, the daily recommended dose of CELEBREX capsules should be reduced by approximately 50% in patients with moderate (Child-Pugh Class II) hepatic impairment. Patients with severe hepatic impairment have not been studied. The use of CELEBREX in patients with severe hepatic impairment is not recommended.

Renal Insufficiency: In a cross-study comparison, celecoxib AUC was approximately 40% lower in patients with chronic renal insufficiency (GFR 35-60 mL/min) than that seen in subjects with normal renal function. No significant relationship was found between GFR and celecoxib clearance. Patients with severe renal insufficiency have not been studied (See Warnings Section: Advanced Renal Disease).

Drug Interactions

Also see **PRECAUTIONS – Drug Interactions.**

General: Significant interactions may occur when celecoxib is administered together with drugs that inhibit P450 2C9. *In vitro* studies indicate that celecoxib is not an inhibitor of cytochrome P450 2C9, 2C19 or 3A4.

Clinical studies with celecoxib have identified potentially significant interactions with fluconazole and lithium. Experience with nonsteroidal anti-inflammatory drugs (NSAIDs) suggests the potential for interactions with furosemide and ACE inhibitors. The effects of celecoxib on the pharmacokinetics and/or pharmacodynamics of glyburide, ketoconazole, methotrexate, phenytoin, and tolbutamide have been studied *in vivo* and clinically important interactions have not been found.

CLINICAL STUDIES

Osteoarthritis (OA): CELEBREX has demonstrated significant reduction in joint pain compared to placebo. CELEBREX was evaluated for treatment of the signs and the symptoms of OA of the knee and hip in approximately 4,200 patients in placebo- and active-controlled clinical trials of up to 12

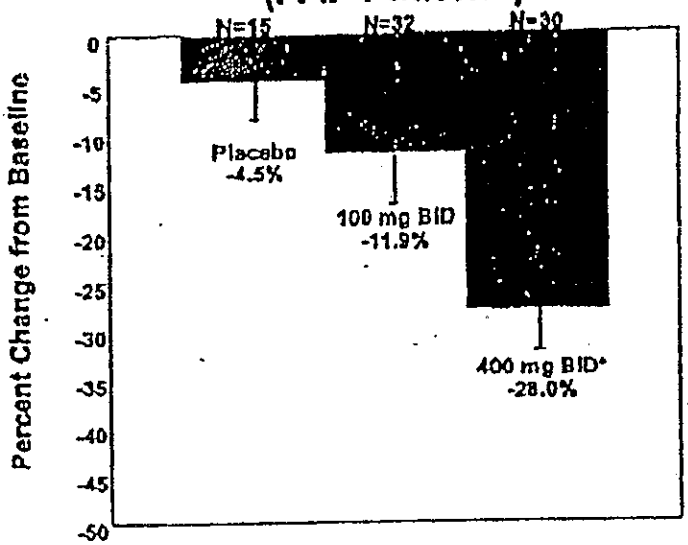
weeks duration. In patients with OA, treatment with CELEBREX 100 mg BID or 200 mg QD resulted in improvement in WOMAC (Western Ontario and McMaster Universities) osteoarthritis index, a composite of pain, stiffness, and functional measures in OA. In three 12-week studies of pain accompanying OA flare, CELEBREX doses of 100mg BID and 200mg BID provided significant reduction of pain within 24-48 hours of initiation of dosing. At doses of 100 mg BID or 200 mg BID the effectiveness of CELEBREX was shown to be similar to that of naproxen 500 mg BID. Doses of 200 mg BID provided no additional benefit above that seen with 100 mg BID. A total daily dose of 200 mg has been shown to be equally effective whether administered as 100 mg BID or 200 mg QD.

Rheumatoid Arthritis (RA): CELEBREX has demonstrated significant reduction in joint tenderness/pain and joint swelling compared to placebo. CELEBREX was evaluated for treatment of the signs and symptoms of RA in approximately 2,100 patients in placebo- and active-controlled clinical trials of up to 24 weeks in duration. CELEBREX was shown to be superior to placebo in these studies, using the ACR20 Responder Index, a composite of clinical, laboratory, and functional measures in RA. CELEBREX doses of 100 mg BID and 200 mg BID were similar in effectiveness and both were comparable to naproxen 500 mg BID.

Although CELEBREX 100 mg BID and 200 mg BID provided similar overall effectiveness, some patients derived additional benefit from the 200 mg BID dose. Doses of 400 mg BID provided no additional benefit above that seen with 100-200 mg BID.

Familial Adenomatous Polyposis (FAP): CELEBREX was evaluated to reduce the number of adenomatous colorectal polyps. A randomized double-blind placebo-controlled study was conducted in 83 patients with FAP. The study population included 58 patients with a prior subtotal or total colectomy and 25 patients with an intact colon. Thirteen patients had the attenuated FAP phenotype. One area in the rectum and up to four areas in the colon were identified at baseline for specific follow-up, and polyps were counted at baseline and following six months of treatment. The mean reduction in the number of colorectal polyps was 28% for CELEBREX 400 mg BID, 12% for CELEBREX 100 mg BID and 5% for placebo. The reduction in polyps observed with CELEBREX 400 mg BID was statistically superior to placebo at the six-month timepoint ($p=0.003$). (See Figure 1.)

Figure 1
Percent Change from Baseline in Number of Colorectal Polyps (FAP Patients)



* p=0.003 versus placebo

Special Studies
Celecoxib Long-term Arthritis Safety Study (CLASS):

Study Design
The primary endpoint of this prospective outcome study was the incidence of ***complicated ulcers*** (gastrointestinal bleeding, perforation or obstruction) in CELEBREX treated patients compared to ibuprofen and diclofenac treated patients. Approximately 5,800 OA patients and 2,200 RA patients were randomized among three treatments. Patients received CELEBREX 400 mg BID (4-fold and 2-fold greater than the recommended OA and RA doses, respectively), ibuprofen 800 mg TID or diclofenac 75 mg BID (common therapeutic doses) for a median exposure of 9 months for Celebrex and diclofenac and 6 months for ibuprofen. Approximately 22% of patients took concomitant low-dose aspirin ($\leq$ 325 mg/day) for cardiovascular prophylaxis.

Study Results
No statistically significant differences were demonstrated for the primary endpoint; incidence of ***complicated ulcers*** among the three treatment groups. An exploratory analysis of ***symptomatic and complicated ulcers*** (perforation, ulcers, and bleeds) did not identify any differences between CELEBREX and the two comparators (ibuprofen and diclofenac). Both analyses are displayed in Table A. Concomitant low-dose aspirin use increased the rates of ***complicated and symptomatic ulcers*** (see section: Use With Aspirin).

Table A

	Celebrex n=1985	diclofenac n=3987	ibuprofen n=1996
Complicated ulcer (Kaplan-Meier cumulative rate in %)	0.7	0.6	0.8
Complicated and symptomatic ulcers (Kaplan- Meier cumulative rate in %)	2.0	1.9	2.8

Event rates in high-risk groups – see section: WARNINGS: Gastrointestinal Effects.

Withdrawals due to adverse events and serious adverse events observed in this trial are shown in Table B.

Table B
Summary of CLASS Safety Data

	Celebrex 400 mg BID n=1985	Diclofenac 75 mg BID n=3987	Ibuprofen 800 mg TID n=1996
Withdrawal due to Adverse Events	22.4	26.5	23.0
*Any Serious Adverse Event	6.8	5.6	6.0

* serious adverse events: A "serious" adverse event is defined as any event that suggests a significant hazard,
contraindication, side effect, or precaution. A serious adverse event includes any event that:

a. Is fatal;
b. Is life threatening, meaning, the subject was, in the view of the Investigator, at immediate risk of death from the reaction as it occurred,
c. Is a persistent or significant disability/incapacity, i.e., the event causes a substantial disruption of a person's ability to conduct normal life functions;
d. Requires, or prolongs, inpatient hospitalization;
e. Is an important medical event, based upon appropriate medical judgment, that may jeopardize the patient or subject or may require medical or surgical intervention to prevent one of the other outcomes defining serious.

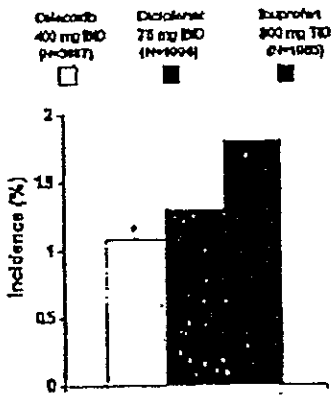
Endoscopic Studies:

The CLASS study described above compared clinically relevant outcomes. Several studies, summarized below, have utilized scheduled endoscopic evaluations to assess the occurrence of asymptomatic ulcers in individual patients taking CELEBREX or a comparator agent. The results of these studies are of uncertain clinical relevance.

Figure 5 and Table 3 summarize data from two 12-week studies that enrolled patients in whom baseline endoscopies revealed no ulcers. Patients underwent interval endoscopies every 4 weeks to give information on ulcer risk over time.

Figure 5
Cumulative Incidence of Gastroduodenal Ulcers Based on 4 Serial Endoscopies over 12 Weeks

Figure 2
Incidence of Symptomatic Ulcers and Ulcer Complications



*p=0.017 vs. ibuprofen

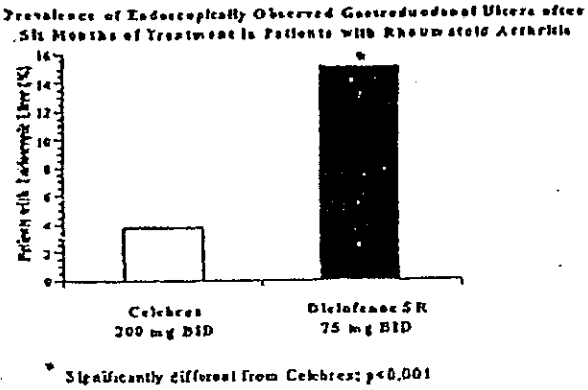
Table 3
Incidence of Gastroduodenal Ulcers from 3-Month Serial Endoscopy Studies in OA and RA Patients

	Week 4	Week 8	Week 12	Final
Study 3 (n=523)				
Celebrex 200 mg BID (20/266)*	4.0% (10/252)*	2.2% (5/227)*	1.5% (3/196)*	7.5%
Naproxen 500 mg BID (89/257)	19.0% (47/247)	14.2% (26/182)	9.9% (14/141)	34.6%
Study 4 (n=1062)				
Celebrex 200 mg BID (25/356)"	3.9% (13/337)"	2.4% (7/296)"	1.8%(5/274)"	7.0%

Diclofenac 75 mg BID (36/372)	5.1% (18/350)	3.3% (10/306)	2.9%(8/278)	9.7%
Ibuprofen 800 mg TID (78/334)	13.0% (42/323)	6.2% (15/241)	9.6% (21/219)	23.3%

*p≤ 0.05 Celebrex vs. naproxen based on interval and cumulative analyses
* p≤ 0.05 Celebrex vs. ibuprofen based on interval and cumulative analyses

One randomized and double-blinded 6-month study in 430 RA patients was conducted in which and endoscopic examination was performed at 6 months. The results are show below:



Use with Aspirin: In the CLASS study, subjects on concomitant low-dose aspirin experienced 4 to 5 fold higher rates of *complicated and symptomatic ulcers.* The results for CELEBREX are displayed in Table C.

Table C

Effects of co-administration of low dose aspirin on *complicated and symptomatic ulcer* rates with Celebrex (Kaplan-meier cumulative % rate)

	Non-aspirin users *n= 3105*	aspirin users *n=882*
Complicated ulcer	*0.4%*	*1.6%*
Complicated and symptomatic	*1.1%*	*4.9%*

In the endoscopic studies described above approximately 11% of patients (440/4,000) enrolled were

taking aspirin (≤ 325 mg of low-dose aspirin/day). In the CELEBREX groups, the endoscopic ulcer rate appeared to be higher in aspirin users than in non-users.

Platelets: In clinical trials, CELEBREX at single doses up to 800 mg and multiple doses of 600 mg BID for up to 7 days duration (higher than recommended therapeutic doses) had no effect on platelet aggregation and bleeding time. Comparators (naproxen 500 mg BID, ibuprofen 800 mg TID, diclofenac 75 mg BID) significantly reduced platelet aggregation and prolonged bleeding time.

INDICATIONS AND USAGE

CELEBREX is indicated:

1) For relief of the signs and symptoms of osteoarthritis.

2) For relief of the signs and symptoms of rheumatoid arthritis in adults.

3) To reduce the number of adenomatous colorectal polyps in familial adenomatous polyposis (FAP), as an adjunct to usual care (e.g., endoscopic surveillance, surgery). It is not known whether there is a clinical benefit from a reduction in the number of colorectal polyps in FAP patients. It is also not known whether the effects of CELEBREX treatment will persist after CELEBREX is discontinued. The efficacy and safety of CELEBREX treatment in patients with FAP beyond six months have not been studied (See CLINICAL STUDIES, WARNINGS and PRECAUTIONS sections).

CONTRAINDICATIONS

CELEBREX is contraindicated in patients with known hypersensitivity to celecoxib.

CELEBREX should not be given to patients who have demonstrated allergic-type reactions to sulfonamides.

CELEBREX should not be given to patients who have experienced asthma, urticaria, or allergic-type reactions after taking aspirin or other NSAIDs. Severe, rarely fatal, anaphylactic-like reactions to NSAIDs have been reported in such patients (see WARNINGS - Anaphylactoid Reactions, and PRECAUTIONS - Preexisting Asthma).

WARNINGS

Gastrointestinal (GI) Effects- Risk of GI Ulceration, Bleeding, and Perforation:

Serious gastrointestinal toxicity such as bleeding, ulceration, and perforation of the stomach, small intestine or large intestine, can occur at any time, with or without warning symptoms, in patients treated with nonsteroidal anti-inflammatory drugs (NSAIDs). Minor upper gastrointestinal problems, such as dyspepsia, are common and may also occur at any time during NSAID therapy. Therefore,

physicians and patients should remain alert for ulceration and bleeding, even in the absence of previous GI tract symptoms. Patients should be informed about the signs and/or symptoms of serious GI toxicity and the steps to take if they occur. The utility of periodic laboratory monitoring has not been demonstrated, nor has it been adequately assessed. Only one in five patients who develop serious upper GI adverse event on NSAID therapy is symptomatic. It has been demonstrated that upper GI ulcers, gross bleeding or perforation, caused by NSAIDs, appear to occur in approximately 1% of patients treated for 3-6 months, and in about 2-4% of patients treated for one year. These trends continue thus, increasing the likelihood of developing a serious GI event at some time during the course of therapy. However, even short-term therapy is not without risk.

NSAIDs should be prescribed with extreme caution in patients with a prior history of ulcer disease or gastrointestinal bleeding. Most spontaneous reports of fatal GI events are in the elderly or debilitated patients and therefore, special care should be taken in treating this population. **To minimize the potential risk for an adverse GI event, the lowest effective dose should be used for the shortest possible duration.** For high risk patients, alternate therapies that do not involve NSAIDs should be considered.

Studies have shown that patients with a prior history of peptic ulcer disease and/or gastrointestinal bleeding and who use NSAIDs, have a greater than 10-fold higher risk for developing a GI bleed than patients with neither of those risk factors. In addition to a past history of ulcer disease, pharmacoepidemiological studies have identified several other co-therapies or co-morbid conditions that may increase the risk of GI bleeding such as : treatment with oral corticosteroids, treatment with anticoagulants, longer duration of NSAID therapy, smoking, alcoholism, older age, and poor general health status.

In the CLASS trial, the rates of *complicated* as well as *complicated and symptomatic ulcers* were higher in subjects over the age of 65 and those with a history of symptomatic peptic ulcer disease. These rates are show in **Table D** below.

Table D (Provided by sponsor)

Kaplan-Meier cumulative rates of complicated and complicated and symptomatic ulcers in patients over age 65 and those with a history of symptomatic peptic ulcer disease in the CLASS trial in subjects treated with CELEBREX 400 mg BID.

	Age over 65 years	Prior history of Symptomatic ulcers
Complicated ulcers		
Complicated and symptomatic ulcers		

Anaphylactoid Reactions
As with NSAIDs in general, anaphylactoid reactions have occurred in patients without known prior exposure to CELEBREX. In post-marketing experience, rare cases of anaphylactic reactions and

angiocdema have been reported in patients receiving CELEBREX. CELEBREX should not be given to patients with the aspirin triad. This symptom complex typically occurs in asthmatic patients who experience rhinitis with or without nasal polyps, or who exhibit severe, potentially fatal bronchospasm after taking aspirin or other NSAIDs (see CONTRAINDICATIONS and PRECAUTIONS - Preexisting Asthma). Emergency help should be sought in cases where an anaphylactoid reaction occurs.

Advanced Renal Disease
No information is available from controlled clinical studies regarding the use of Celebrex in patients with advanced renal disease. In post-marketing experience, serious renal failure, including the need for dialysis and fatalities, have been reported in patients with normal, as well as impaired renal function. Therefore, the treatment with CELEBREX is not recommended in patients with advanced renal disease. Kidney function should be monitored, especially in high risk populations, such as the elderly, patients with cardiovascular disease and diabetes mellitus, as well as in the setting of concomitant use of diuretics and ACE inhibitors.

Pregnancy
In late pregnancy CELEBREX should be avoided because it may cause premature closure of the ductus arteriosus.

Familial Adenomatous Polyposis (FAP): Treatment with CELEBREX in FAP has not been shown to reduce the risk of gastrointestinal cancer or the need for prophylactic colectomy or other FAP-related surgeries. Therefore, the usual care of FAP patients should not be altered because of the concurrent administration of CELEBREX. In particular, the frequency of routine endoscopic surveillance should not be decreased and prophylactic colectomy or other FAP-related surgeries should not be delayed.

PRECAUTIONS

General: CELEBREX cannot be expected to substitute for corticosteroids or to treat corticosteroid insufficiency. Abrupt discontinuation of corticosteroids may lead to exacerbation of corticosteroid-responsive illness. Patients on prolonged corticosteroid therapy should have their therapy tapered slowly if a decision is made to discontinue corticosteroids.

The pharmacological activity of CELEBREX in reducing inflammation, and possibly fever, may diminish the utility of these diagnostic signs in detecting infectious complications of presumed noninfectious, painful conditions.

Hepatic Effects: Borderline elevations of one or more liver tests may occur in up to 15% of patients taking NSAIDs, and notable elevations of ALT or AST (approximately three or more times the upper limit of normal) have been reported in approximately 1% of patients in clinical trials with NSAIDs. These laboratory abnormalities may progress, may remain unchanged, or may be transient with continuing therapy. Rare cases of severe hepatic reactions, including jaundice and fatal fulminant hepatitis, liver necrosis and hepatic failure (some with fatal outcome) have been reported with NSAIDs, including CELEBREX. (See ADVERSE REACTIONS – post-marketing experience.) In

controlled clinical trials of CELEBREX, the incidence of borderline elevations of liver tests was 6% for CELEBREX and 5% for placebo, and approximately 0.2% of patients taking CELEBREX and 0.3% of patients taking placebo had notable elevations of ALT and AST.

A patient with symptoms and/or signs suggesting liver dysfunction, or in whom an abnormal liver test has occurred, should be monitored carefully for evidence of the development of a more severe hepatic reaction while on therapy with CELEBREX. If clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur (e.g., eosinophilia, rash, etc.), CELEBREX should be discontinued.

Renal Effects: Long-term administration of NSAIDs has resulted in renal papillary necrosis and other renal injury. Renal toxicity has also been seen in patients in whom renal prostaglandins have a compensatory role in the maintenance of renal perfusion. In these patients, administration of a nonsteroidal anti-inflammatory drug may cause a dose-dependent reduction in prostaglandin formation and, secondarily, in renal blood flow, which may precipitate overt renal decompensation. Patients at greatest risk of this reaction are those with impaired renal function, heart failure, liver dysfunction, those taking diuretics and ACE inhibitors, and the elderly. Discontinuation of NSAID therapy is usually followed by recovery to the pretreatment state. Clinical trials with CELEBREX have shown renal effects similar to those observed with comparator NSAIDs.

Caution should be used when initiating treatment with CELEBREX in patients with considerable dehydration. It is advisable to rehydrate patients first and then start therapy with CELEBREX. Caution is also recommended in patients with pre-existing kidney disease (see WARNINGS-Advanced Renal Disease).

Hematological Effects: Anemia is sometimes seen in patients receiving CELEBREX. In controlled clinical trials the incidence of anemia was 0.6% with CELEBREX and 0.4% with placebo. Patients on long-term treatment with CELEBREX should have their hemoglobin or hematocrit checked if they exhibit any signs of symptoms of anemia or blood loss. CELEBREX does not generally affect platelet counts, prothrombin time (PT), or partial thromboplastin time (PTT), and does not appear to inhibit platelet aggregation at indicated dosages (See CLINICAL STUDIES – Special Studies Platelets).

Fluid Retention and Edema: Fluid retention and edema have been observed in some patients taking CELEBREX (see ADVERSE REACTIONS). Therefore, CELEBREX should be used with caution in patients with fluid retention, hypertension, or heart failure.

Preexisting Asthma: Patients with asthma may have aspirin-sensitive asthma. The use of aspirin in patients with aspirin-sensitive asthma has been associated with severe bronchospasm which can be fatal. Since cross reactivity, including bronchospasm, between aspirin and other nonsteroidal anti-inflammatory drugs has been reported in such aspirin-sensitive patients, CELEBREX should not be administered to patients with this form of aspirin sensitivity and should be used with caution in patients with preexisting asthma.

Information for Patients: CELEBREX can cause discomfort and, rarely, more serious side effects, such as gastrointestinal bleeding, which may result in hospitalization and even fatal outcomes. Although serious GI tract ulcerations and bleeding can occur without warning symptoms, patients

should be alert for the signs and symptoms of ulcerations and bleeding, and should ask for medical advice when observing any indicative signs or symptoms. Patients should be apprised of the importance of this follow-up (see WARNINGS, Risk of Gastrointestinal Ulceration, Bleeding and Perforation).

Patients should promptly report signs or symptoms of gastrointestinal ulceration or bleeding, skin rash, unexplained weight gain, or edema to their physicians.

Patients should be informed of the warning signs and symptoms of hepatotoxicity (e.g., nausea, fatigue, lethargy, pruritus, jaundice, right upper quadrant tenderness, and "flu-like" symptoms). If these occur, patients should be instructed to stop therapy and seek immediate medical therapy.

Patients should also be instructed to seek immediate emergency help in the case of an anaphylactoid reaction (see WARNINGS).

In late pregnancy CELEBREX should be avoided because it may cause premature closure of the ductus arteriosus.

Patients with familial adenomatous polyposis (FAP) should be informed that CELEBREX has not been shown to reduce colorectal, duodenal or other FAP-related cancers, or the need for endoscopic surveillance, prophylactic or other FAP-related surgery. Therefore, all patients with FAP should be instructed to continue their usual care while receiving CELEBREX.

Laboratory Tests: Because serious GI tract ulcerations and bleeding can occur without warning symptoms, physicians should monitor for signs or symptoms of GI bleeding.

During the controlled clinical trials, there was an increased incidence of hyperchloremia in patients receiving celecoxib compared with patients on placebo. Other laboratory abnormalities that occurred more frequently in the patients receiving celecoxib include hypophosphotemia, and elevated BUN. The clinical significance of these abnormalities has not been established.

In controlled clinical trials elevated BUN occurred more frequently in patients receiving CELEBREX compared with patients on placebo. This abnormality was also seen in patients who received comparator NSAIDs in these studies.

Drug Interactions

General: Celecoxib metabolism is predominantly mediated via cytochrome P450 2C9 in the liver. Co-administration of celecoxib with drugs that are known to inhibit 2C9 should be done with caution.

In vitro studies indicate that celecoxib, although not a substrate, is an inhibitor of cytochrome P450 2D6. Therefore, there is a potential for an *in vivo* drug interaction with drugs that are metabolized by P450 2D6.

ACE-inhibitors: Reports suggest that NSAIDs may diminish the antihypertensive effect of Angiotensin Converting Enzyme (ACE) inhibitors. This interaction should be given consideration in

patients taking CELEBREX concomitantly with ACE-inhibitors.

Furosemide: Clinical studies, as well as post marketing observations, have shown that NSAIDs can reduce the natriuretic effect of furosemide and thiazides in some patients. This response has been attributed to inhibition of renal prostaglandin synthesis.

Aspirin: CELEBREX can be used with low dose aspirin. However, concomitant administration of aspirin with CELEBREX may result in an increased rate of GI ulceration or other complications, compared to use of CELEBREX alone.

Because of its lack of platelet effects, CELEBREX is not a substitute for aspirin for cardiovascular prophylaxis.

Fluconazole: Concomitant administration of fluconazole at 200 mg QD resulted in a two-fold increase in celecoxib plasma concentration. This increase is due to the inhibition of celecoxib metabolism via P450 2C9 by fluconazole (see Pharmacokinetics - Metabolism). CELEBREX should be introduced at the lowest recommended dose in patients receiving fluconazole.

Lithium: In a study conducted in healthy subjects, mean steady-state lithium plasma levels increased approximately 17% in subjects receiving lithium 450 mg BID with CELEBREX 200 mg BID as compared to subjects receiving lithium alone. Patients on lithium treatment should be closely monitored when CELEBREX is introduced or withdrawn.

Methotrexate: In an interaction study of rheumatoid arthritis patients taking methotrexate, CELEBREX did not have a significant effect on the pharmacokinetics of methotrexate.

Warfarin: Anticoagulant activity should be monitored, particularly in the first few days after initiating or changing CELEBREX therapy in patients receiving warfarin or similar agents, since these patients are at an increased risk of bleeding complications. The effect of celecoxib on the anti-coagulant effect of warfarin was studied in a group of healthy subjects receiving daily doses of 2-5 mg of warfarin. In these subjects, celecoxib did not alter the anticoagulant effect of warfarin as determined by prothrombin time. However, in post-marketing experience, bleeding events have been reported, predominantly in the elderly, in association with increases in prothrombin time in patients receiving CELEBREX concurrently with warfarin.

Carcinogenesis, mutagenesis, impairment of fertility: Celecoxib was not carcinogenic in rats given oral doses up to 200 mg/kg for males and 10 mg/kg for females (approximately 2- to 4-fold the human exposure as measured by the AUC_{0-24} at 200 mg BID) or in mice given oral doses up to 25 mg/kg for males and 50 mg/kg for females (approximately equal to human exposure as measured by the AUC_{0-24} at 200 mg BID) for two years.

Celecoxib was not mutagenic in an Ames test and a mutation assay in Chinese hamster ovary (CHO) cells, nor clastogenic in a chromosome aberration assay in CHO cells and an *in vivo* micronucleus test in rat bone marrow.
Celecoxib did not impair male and female fertility in rats at oral doses up to 600 mg/kg/day (approximately 11-fold human exposure at 200 mg BID based on the

Adverse events from the original controlled arthritis trials: Table 4 lists all adverse events, regardless of causality, occurring in ≥2% of patients receiving CELEBREX from 12 controlled studies conducted in patients with OA or RA that included a placebo and/or a positive control group.

Table 4

Adverse Events Occurring in ≥2% Of Celebrex Patients From Controlled Arthritis Trials

	Celebrex (100-200 mg BID or 200 mg QD) (N=4146)	Placebo (N=1864)	Naproxen 500 mg BID (N=1366)	Diclofenac 75 mg BID 800 mg TID (N=387)	Ibuprofen (N=345)
Gastrointestinal					
Abdominal pain	4.1%	2.8%	7.7%	9.0%	9.0%
Diarrhea	5.6%	3.8%	5.3%	9.3%	5.8%
Dyspepsia	8.8%	6.2%	12.2%	10.9%	12.8%
Flatulence	2.2%	1.0%	3.6%	4.1%	3.5%
Nausea	3.5%	4.2%	6.0%	3.4%	6.7%
Body as a whole					
Back Pain	2.8%	3.6%	2.2%	2.6%	0.9%
Peripheral edema	2.1%	1.1%	2.1%	1.0%	3.5%
Injury-accidental	2.9%	2.3%	3.0%	2.6%	3.2%
Central and peripheral nervous system					
Dizziness	2.0%	1.7%	2.6%	1.3%	2.3%
Headache	15.8%	20.2%	14.5%	15.5%	15.4%
Psychiatric					
Insomnia	2.3%	2.3%	2.9%	1.3%	1.4%
Respiratory					
Pharyngitis	2.3%	1.1%	1.7%	1.6%	2.6%
Rhinitis	2.0%	1.3%	2.4%	2.3%	0.6%
Sinusitis	5.0%	4.3%	4.0%	5.4%	5.8%
Upper respiratory tract infection	8.1%	6.7%	9.9%	9.8%	9.9%
Skin					
Rash	2.2%	2.1%	2.1%	1.3%	1.2%

In placebo- or active-controlled clinical trials, the discontinuation rate due to adverse events was 7.1% for patients receiving CELEBREX and 6.1% for patients receiving placebo. Among the most common reasons for discontinuation due to adverse events in the CELEBREX treatment groups were dyspepsia and abdominal pain (cited as reasons for discontinuation in 0.8% and 0.7% of CELEBREX patients, respectively). Among patients receiving placebo, 0.6% discontinued due to dyspepsia and 0.6% withdrew due to abdominal pain.

The adverse event profile of CELEBREX 400 mg BID (4-fold and 2-fold the recommended doses for OA and RA, respectively) from the long-term outcomes trial was similar to that reported in the arthritis controlled trials.

The following adverse events occurred in 0.1 - 1.9% of patients regardless of causality.

Celebrex
(100 - 200 mg BID or 200 mg QD)

Gastrointestinal:	Constipation, diverticulitis, dysphagia, eructation, esophagitis, gastritis, gastroenteritis, gastroesophageal reflux, hemorrhoids, hiatal hernia, melena, dry mouth, stomatitis, tenesmus, tooth disorder, vomiting
Cardiovascular:	Aggravated hypertension, angina pectoris, coronary artery disorder, myocardial infarction
General:	Allergy aggravated, allergic reaction, asthenia, chest pain, cyst NOS, edema generalized, face edema, fatigue, fever, hot flushes, influenza-like symptoms, pain, peripheral pain
Resistance mechanism disorders:	Herpes simplex, herpes zoster, infection bacterial, infection fungal, infection soft tissue, infection viral, moniliasis, moniliasis genital, otitis media
Central, peripheral nervous system:	Leg cramps, hypertonia, hypoesthesia, migraine, neuralgia, neuropathy, paresthesia, vertigo
Female reproductive:	Breast fibroadenosis, breast neoplasm, breast pain, dysmenorrhea, menstrual disorder, vaginal hemorrhage, vaginitis
Male reproductive:	Prostatic disorder
Hearing and vestibular:	Deafness, ear abnormality, earache, tinnitus
Heart rate and rhythm:	Palpitation, tachycardia
Liver and biliary system:	Hepatic function abnormal, SGOT increased, SGPT increased
Metabolic and nutritional:	BUN increased, CPK increased, diabetes mellitus, hypercholesterolemia, hyperglycemia, hypokalemia, NPN increase, creatinine increased, alkaline phosphatase increased, weight increase
Musculoskeletal:	Arthralgia, arthrosis, bone disorder, fracture accidental, myalgia, neck stiffness, synovitis, tendinitis
Platelets (bleeding or clotting):	Ecchymosis, epistaxis, thrombocythemia
Psychiatric:	Anorexia, anxiety, appetite increased, depression, nervousness, somnolence
Hemic:	Anemia
Respiratory:	Bronchitis, bronchospasm, bronchospasm aggravated, coughing, dyspnea, laryngitis, pneumonia
Skin and appendages:	Alopecia, dermatitis, nail disorder, photosensitivity reaction, pruritus, rash erythematous, rash maculopapular, skin disorder, skin dry, sweating increased, urticaria
Application site disorders:	Cellulitis, dermatitis contact, injection site reaction, skin nodule
Special senses:	Taste perversion
Urinary system:	Albuminuria, cystitis, dysuria, hematuria, micturition frequency, renal calculus, urinary incontinence, urinary tract infection
Vision:	Blurred vision, cataract, conjunctivitis, eye pain, glaucoma

Other serious adverse reactions which occur rarely (estimated <0.1%), regardless of causality: The following serious adverse events have occurred rarely in patients, taking CELEBREX. Cases reported only in the post-marketing experience are indicated in italics.

Cardiovascular:	Syncope, congestive heart failure, ventricular fibrillation, pulmonary embolism, cerebrovascular accident, peripheral gangrene thrombophlebitis, *vasculitis*

Gastrointestinal: Intestinal obstruction, intestinal perforation, gastrointestinal bleeding, colitis with bleeding, esophageal perforation, pancreatitis, ileus

Liver and biliary system: Cholelithiasis, *hepatitis, jaundice, liver failure*

Hemic and lymphatic: Thrombocytopenia, *agranulocytosis, aplastic anemia, pancytopenia, leukopenia*

Metabolic: *Hypoglycemia*

Nervous system: Anxia, suicide

Renal: Acute renal failure, *interstitial nephritis*

Skin: *Erythema multiforme, exfoliative dermatitis, Stevens-Johnson syndrome, toxic epidermal necrolysis*

General: Sepsis, sudden death, *anaphylactoid reaction, angioedema*

Data on withdrawals due to adverse events and serious adverse events seen in the CLASS trial, regardless of causality, are displayed in tables 5 and 6. The CLASS study, as described in the *Special Studies Section*, was designed to assess the chronic safety of CELEBREX at 400mg BID, the approved dose for FAP (median exposure to CELEBREX was 9 months).

Table 5
Withdrawals Due to Adverse Events (%)*

	Celebrex	Diclofenac	Ibuprofen
Any Event	22.4	26.5	23.0
Abdominal pain	4.3	6.5	4.9
Dyspepsia	3.8	4.4	3.9
Rash	2.1	0.7	1.3
Nausea	1.7	2.8	1.8
Diarrhea	1.4	2.7	0.8
Transaminase Elevation	0.1	2.1	0.1

* Incidence >1% in any treatment group

Table 6
Serious Adverse Events

	Celebrex	Diclofenac	Ibuprofen
Any serious Event (%)	11.6	10.3	10.6
Abdominal Pain	0.3	0.6	0.2
Unstable Angina	0.3	0.4	0
Myocardial Infarction	0.8	0.4	0.8
Cerebrovascular Disorder	0.2	0.6	0.5
Cardiac Failure	0.4	0.2	0.8
Cellulitis	0.3	<0.1	<0.1

Adverse events from the controlled trial in familial adenomatous polyposis: The adverse event profile reported for the 83 patients with familial adenomatous polyposis enrolled in the randomized, controlled clinical trial was similar to that reported for patients in the arthritis controlled trials. Intestinal anastomotic ulceration was the only new adverse event reported in the FAP trial, regardless of causality, and was observed in 3 of 58 patients (one at 100 mg BID, and two at 400 mg BID) who had prior intestinal surgery.

OVERDOSAGE

Doses of 2400 mg/day ingested for up to 10 days did not result in serious toxicity.

Patients should be managed by symptomatic and supportive care following an NSAID overdose. There are no specific antidotes. No information is available regarding the removal of celecoxib by hemodialysis, but based on its high degree of plasma protein binding (>97%) dialysis is unlikely to be useful in overdose. Emesis and/or activated charcoal (60 to 100 g in adults, 1 to 2 g/kg in children) and/or osmotic cathartic may be indicated in patients seen within 4 hours of ingestion with symptoms or following a large overdose. Forced diuresis, alkalinization of urine, hemodialysis, or hemoperfusion may not be useful due to high protein binding.

DOSAGE AND ADMINISTRATION

For osteoarthritis and rheumatoid arthritis, the lowest dose of CELEBREX should be sought for each patient. These doses can be given without regard to timing of meals.

Osteoarthritis: For relief of the signs and symptoms of osteoarthritis the recommended oral dose is 200 mg per day administered as a single dose or as 100 mg twice per day.

Rheumatoid arthritis: For relief of the signs and symptoms of rheumatoid arthritis the recommended oral dose is 100 to 200 mg twice per day.

Familial adenomatous polyposis (FAP): Usual medical care for FAP patients should be continued while on CELEBREX. To reduce the number of adenomatous colorectal polyps in patients with FAP, the recommended oral dose is 400 mg (2 X 200 mg capsules) twice per day to be taken with food.

Special Populations

Hepatic insufficiency: The daily recommended dose of CELEBREX capsules in patients with moderate hepatic impairment (Child-Pugh Class II) should be reduced by approximately 50% (see CLINICAL PHARMACOLOGY – Special Populations).

HOW SUPPLIED

CELEBREX 100-mg capsules are white, reverse printed white on blue band of body and cap with markings of 7767 on the cap and 100 on the body, supplied as:

NDC Number	Size
0025-1520-31	bottle of 100
0025-1520-51	bottle of 500
0025-1520-34	carton of 100 unit dose

CELEBREX 200-mg capsules are white, with reverse printed white on gold band with markings of 7767 on the cap and 200 on the body, supplied as:

NDC Number	Size
0025-1525-31	bottle of 100
0025-1525-51	bottle of 500
0025-1525-34	carton of 100 unit dose

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [See USP Controlled Room Temperature]

Rx only Revised: 04/05/01

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EXHIBIT 14

CREDIT SUISSE FIRST BOSTON CORPORATION
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BUY
Target Price: 50.00 (US$)
Pharmacia Corporation (PHA)
FDA Approves Celebrex Improved Gastrointestinal Safety Labeling

Summary

The FDA has approved improved gastrointestinal safety labeling for Celebrex tied to favorable results from the CLASS clinical trial. The label also includes new information on cardiovascular safety, hypertension, edema and hematologic events.

The label will now reflect Celebrex's superior profile in reducing the risk of serious gastrointestinal (GI) side effects relative to diclofenac and ibuprofen. As a primary point of differentiation, the revised label also states that Celebrex is not associated with any increase in serious adverse cardiovascular events compared to these NSAIDs.

The revised label represents a significant advantage over Merck's (MRK $52.80, Hold; TP $65) Vioxx label, which was recently modified to contain precautionary wording on the increased incidence of cardiovascular events.

We believe the Celebrex labeling change will benefit the ongoing conversion of traditional NSAID users into the COX-2 class as well as provide Pharmacia/Pfizer (PFE $34.78, Buy; TP $49) with an additional advantage in the battle for market share within the category

We are retaining our Celebrex 2002 sales forecast at $2.92 billion. On a collective franchise basis, we are now assuming that Pharmacia will generate about $3.46 billion in overall COX-2 franchise sales in 2002, up about 11% over the 2001 level of $3.11 billion.

Pharmacia's earnings profile remains poised for acceleration moving into 2003, supported by the COX-2 franchise as well as the expected launch of eplerenone into the U.S. hypertension market. We continue to rate the stock buy with a 12-month target price of $50.

Price	Target			Mkt. Value	52-Week	
06 Jun 02	(12mo.)	Div	Yield(%)	($m)	Price Range	
38.90($)	50.00($)			50,302.33	51.50 - 37.50	
	Annual			Rel.	EBITDA	EV/
	EPS($)	Prev. EPS	Abs. P/E(x)	P/E(%)	($m)	EBITDA(x)
12/03E	1.81		21.5	132.4		
12/02E	1.54		25.3	129.8		
12/01A	1.51		25.8	117.1	2,166.4	23.2
	Q1	Q2	Q3	Q4		
2003E	0.37	0.46	0.52	0.46		
2002E	0.31	0.40	0.45	0.38		
2001A	0.29	0.38	0.45	0.38		
ROIC(12/01A %)				11.1%		
Net debt(12/01A $m)						
Net debt/Total cap.(12/01A %)						
Book value/share(12/01A)						
Number of Shares(m)				1,293.12		

1On 06/06/02 the S&P 500 index closed at 1029.15.
2Economic profit trend.

Pharmacia is a leading global pharmaceutical company created through the merger of Pharmacia & Upjohn with Monsanto Company and its G.D. Searle unit.

Investment Summary

Pharmacia announced that the FDA has approved changes to the Celebrex label to include results from the CLASS(Celecoxib Long-term Arthritis Safety Study) clinical trial as well as the new information about cardiovascular safety, hypertension, edema and hematologic events.

The label reflects Celebrex's superior profile in reducing the risk of serious gastrointestinal(GI) side effects compared to diclofenac and ibuprofen. Perhaps more importantly, the revised label states that there is no increased risk for serious adverse cardiovascular events with Celebrex relative to these comparator NSAIDs(diclofenac and ibuprofen).

The revision occurs at the end of a turbulent week for the COX-2 inhibitor category. Early in the week, Celebrex was criticized in the British Medical Journal for failing to report the full 12 months of trial data for the CLASS trial. Managed care companies such as Express Scripts also publicly chastised the COX-2 inhibitors, complaining on the appropriateness and cost-effectiveness of use across broad patient groups.

We believe the label revision provides FDA validation on both the conclusions of the CLASS trial as well as points of positive differentiation for Celebrex relative to its main competitor, Merck's Vioxx. The revised Celebrex label represents a significant advantage over Merck's Vioxx label, which was recently modified to contain precautionary wording on the increased incidence of cardiovascular events.

The new label includes data from the CLASS clinical trial through nine months of treatment, representing the median duration of exposure for Celebrex and diclofenac groups, with no safety signals beyond this timepoint. Data in the label indicates the estimated cumulative incidence of upper gastrointestinal(GI) complicated and symptomatic ulcers for patients treated with Celebrex for one year is 0.78%(compared with an incidence of 2-4% in NSAID treated patients) even at higher doses than the FDA approved for Celebrex in the treatment of osteoarthritis(OA) and rheumatoid arthritis(RA). Estimated cumulative incidence of upper GI complicated ulcers was 0.32% in the Celebrex non-aspirin users.

CLASS Clinical Trial Background

Recent Publication of 12-Month CLASS Data

Pharmacia recently published the full 12-month data set for the Celebrex Long-term Arthritis Safety Study(CLASS). This follows the original publication of 6-month data, which provided the foundation of CLASS in the September 13, 2000 Journal of the American Medical Association(JAMA). In February 2001, the FDA evaluated the 6-month trial results, which assessed Celebrex's profile of superior gastrointestinal safety compared with ibuprofen and diclofenac.

At the time of the original JAMA publication, controversy developed over the availability of 12-month data tied to the CLASS clinical trial. The data was not provided to JAMA, largely because Pharmacia had not fully completed data analysis.

Pharmacia indicated that after the unblinding of the 12-month data, study drop-outs(confined to primarily ibuprofen and diclofenac users) yielded a different study population in the second half of the trial. This dropout rate also distorted statistical powering, since the original study was designed to have 15% of participants with peptic ulcer disease, 3% with past gastrointestinal bleeding history and 55% with cardiovascular disease. The actual data showed only 8% with peptic ulcer disease, 1.5% with GI bleeding history and 40% with

cardiovascular disease.

CLASS published annualized figures, based on six-month data, showing an incidence of upper GI complications in Celebrex users of 0.78%(11 events/1,441 patient-years) vs. an incidence of 1.45%(20 events/1,384 patient years) for patients taking NSAIDS(p=0.09).

Pharmacia originally received an "approvable" letter from the FDA last spring for improved Celebrex labeling.

Current COX-2 Market Dynamics

We believe that Pharmacia(and its marketing partner, Pfizer) have the upper hand in the COX-2 inhibitor marketing battle. Prescription uptake for the new Bextra(Pharmacia's second generation COX-2 inhibitor) is showing a strong start, which has also allowed Pharmacia to actually increase its relative share position in the collective COX-2/NSAID category. This runs counter to original worries that Bextra would largely cannabalize Celebrex prescription activity.

We believe that Pharmacia will continue to promote the relative cardiovascular safety profile of both its COX-2 inhibitor product lines, Celebrex and Bextra, as being superior to Merck's Vioxx.

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EXHIBIT 15

February 7, 2001

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Pharmacia (BUY)
Pfizer (BUY)

FDA REVIEW OF CELEBREX MORE NEGATIVE THAN EXPECTED – PANEL COULD BE CONTROVERSIAL

PHA			Earnings Per Share				P/E			
2/06	52-Wk Rge	12/00	12/01	12/02	1Q/01	1Q/00	12/00A	12/01E	Yld	MktCap ($MM)
$57.65	$64-35	$1.44E	$1.78E	$2.20E	$0.40E	$0.33A	40.0	32.4	0.8%	74,300
PFE										
$45.85	$49-30	$1.02A	$1.31E	$1.61E	$0.31E	$0.25A	45.0	35.0	1.0%	289,300

Summary

- **The FDA's written review of the Celebrex sNDA seeking modification or elimination of the NSAID class label was issued yesterday (in advance of today's FDA Advisory Panel Meeting). These reports are more negative than anticipated, raising the possibility of a contentious Advisory Panel review today.**

- **The FDA raised four key issues:** (1) Pharmacia's choice to analyze the 26 week data exclusively (vs. 52 week data) is incorrect; (2) Celebrex failed to show any statistically significant benefit over one of the comparator NSAIDs (diclofenac); (3) Pharmacia failed to adjust for multiple subgroup analyses, rendering even those P values less than 0.05 in doubt; and (4) ibuprofen plus aspirin was statistically superior to either Celebrex or diclofenac plus aspirin (and better than ibuprofen alone).

- **Although we have not been expecting the FDA to entirely do away with the NSAID GI warning, we have expected modifications to the label,** including at least a summary of the CLASS trial results, which we believed would be a positive development. Although the ultimate outcome (what the FDA will require in the label) is hard to predict and there is always room for an upside surprise (witness PFE's Zeldox), the FDA's review has to raise investor concerns.

Additional information is available upon request.

- **Clearly, this meeting is not likely to be clear sailing for Celebrex.** We anticipated plenty of debate between the statistical sticklers (typically the FDA) and the real world pragmatists (typically the Advisory Committee); however, the issue of statistical proof of GI superiority vs. NSAIDs appears thornier than we initially thought. The degree of label improvement may be less dramatic than hoped, and the ability to extrapolate superiority vs. one NSAID (i.e. ibuprofen) to "all NSAIDs" may be limited.

- **Often the FDA review of data is gloomier than the Advisory Committee dialogue (to occur later today), so we will have to wait for the meetings today and tomorrow (for Vioxx) to get clear punchlines. We still view similar label revisions for both products, with both able to boost their NSAID superiority claim as the "most likely" outcome, but based on the FDA review of the Celebrex data, risks to that view have grown**

Details

- Following a review of the FDA briefing documents for today's Arthritis Advisory Committee Meeting to consider label modifications for Celebrex, **we believe that this meeting is likely to be more controversial than expected as the FDA took issue with some Pharmacia analyses of the GI benefits of Celebrex versus NSAIDS.**

- **It has been well-known that the CLASS trial, designed to prove a safety advantage for Celebrex, showed a strong trend on the primary endpoint (upper GI complications, also referred to as POBs) that did not achieve statistical significance.** Investors have taken some comfort in additional measures in the trial, in particular, a statistically significant improvement over the NSAID comparators was seen on the secondary endpoint of upper GI events plus gastroduodenal ulcers (also referred to as PUBs) and a statistically significant safety advantage over NSAIDs in the subgroup of patients not taking aspirin (about 80% of the total).

- **Although our expectation has not been that the FDA would do away entirely with the NSAID GI warning, we have expected that there would be some modification of the label.** We have believed that this modification would include at least a summary of the CLASS trial results. The extent of label modification will determine the path of future marketing efforts, both by sales reps and in DTC campaigns.

- **Several new issues emerged in the FDA's analysis that should cause concern for investors and raise questions over how improved the new label will be.** These concerns were raised by the Medical Officer's review, the Gastrointestinal Medical Officer's review, and in the statistical review, with the latter two reviews a bit more harsh.

- The four main issues raised by the FDA are: **(1) Pharmacia's analysis of data at only the 26 week time point, rather than the 52 week time point, is unjustified and invalid** (and the data is even less robust at 52 weeks); **(2) in every subgroup at every time point, Celebrex failed to show a statistically significant benefit over doclofenac** (the benefit reported over NSAIDS is due mostly to the benefit over ibuprofen); **(3) even in subgroups in which Celebrex appeared statistically significantly superior to ibuprofen, the P values are uninterpretable owing to a failure to adjust for multiple subgroup analyses;** and **(4) ibuprofen plus aspirin was statistically superior to either Celebrex or diclofenac plus aspirin** (and better than ibuprofen alone).

Additional information is available upon request.

The 26 Week Time Point

- Pharmacia's rationale for looking at the 26 week data only was that the greater withdrawal of patients from the diclofenac arm "censored" later events (i.e., patients on diclofenac were more likely to develop symptoms and thus were disproportionately removed from the trial before having a chance to develop a serious upper GI events.)

- **The Gastroenterology Medical Review Officer rejected Pharmacia's rationale for a number of reasons,** the most compelling of which in our view are that: **(1)** if diclofenac does produce symptoms that lead to discontinuation of the drug (thus preventing the development of serious upper GI events), then one would not want to minimize this effect in comparing Celebrex to diclofenac; **(2)** despite the higher drop-out rate for diclofenac, a similar event rate pattern was seen for ibuprofen, suggesting that the diclofenac drop-out rate did not actually affect the diclofenac event rate; **(3)** the decision to analyze the 26 week data was post hoc and was made after it was clear that the event rate in the NSAID groups, but not in the Celebrex group, slowed after 26 weeks; **(4)** any true bias resulting from the increased diclofenac withdrawal rate is not adequately addressed by choosing the 26 week data point; and **(5)** there is little evidence from the trial or from the medical literature suggesting that complicated NSAID-related ulcers are associated with prior symptoms.

- **Both the Gastrointestinal Reviewer and the Statistical Reviewer so strongly disagreed with Pharmacia's analysis of the data at the 26 week time point that both specifically did not discuss or treat those results, focusing instead their entire discussion on the end-of-study data.**

- **Because the event rates for diclofenac and ibuprofen plateaued after 26 weeks but continued to rise for Celebrex, the differences between Celebrex and the comparators was less robust at the end-of-study time point.** In particular, the statistically significant reduction in the primary endpoint (serious upper GI events) seen in the non-aspirin subgroup at 26 weeks is not statistically significant at 52 weeks (Table 1).

Table 1: Statistical Significance in the FDA's Analysis of the CLASS Trial

Comparator	Time Point	Population	Primary Endpoint (POBs)	Secondary Endpoint (PUBs)
Ibuprofen + diclofenac	26 weeks	Total study	Not significant	$p = 0.023$
		Not taking aspirin	$p = 0.037$	$p = 0.017$
	End-of-study	Total study	Not significant	$p = 0.040$
		Not taking aspirin	Not significant	$p = 0.020$
Ibuprofen	26 weeks	Total study	Not significant	$p = 0.005$
		Not taking aspirin	$p = 0.020$	$p < 0.001$
	End-of-study	Total study	Not significant	$p = 0.017$
		Not taking aspirin	$p = 0.037$	$p < 0.001$
Diclofenac	26 weeks	Total study	Not significant	Not significant
		Not taking aspirin	Not significant	Not significant
	End-of-study	Total study	Not significant	Not significant
		Not taking aspirin	Not significant	Not significant

Source: FDA Medical Officers Review

Additional information is available upon request.

The Failure Versus Diclofenac

- As illustrated in Table 1, **Celebrex was not statistically superior to diclofenac on any measure at any time point in any subgroup. This is particularly surprising because diclofenac (Novartis' Voltaren) is generally viewed as tougher on the GI than ibuprofen. Intuitively, this supports PHA's contention that there is a diclofenac dropout problem, but the FDA statisticians dispute this.**

- This has obvious implications for those hoping for a complete removal of the NSAID class warning. In the words of the Medical Officer, "for making drug class (i.e. COX-2 vs. NSAIDs) comparisons, it could be argued that beating one NSAID does not mean you beat them all, but losing to one NSAID (or failing to beat it) is losing to them all."

Failure to Adjust for P Values

- **Both the Gastrointestinal Reviewer and the Statistical Reviewer also questioned the p values calculated by Pharmacia, as these calculations (see Table 1) do not account for the multiple subgroup analyses and comparisons performed in the data analysis.** Such manipulations have the effect of raising p values. **On this basis, both of these reviews (in contrast to the Medical Officer review) question the statistical superiority of Celebrex over ibuprofen (and both NSAIDs combined) shown for the secondary endpoint.**

The Aspirin Effect

- Paradoxically, patients taking ibuprofen and aspirin had fewer events than did those taking ibuprofen alone. **The event rate in patients taking ibuprofen and aspirin was statistically superior to the event rate seen in patients taking Celebrex plus aspirin and in patients taking diclofenac plus aspirin.**

Table 2: Event Rates in Patients On and Off Aspirin

Event Rates	Celebrex	Ibuprofen	Diclofenac	Ibuprofen + Diclofenac
Total Population	0.43%	0.55%	0.50%	0.53%
Not taking aspirin	0.26%	0.64%	0.26%	0.45%
Taking aspirin	1.02%	0.26%	1.35%	0.85%

Source: Medical Officer Review.

- The reviewers have trouble explaining this phenomenon, suggesting that the interaction with aspirin may not be a class effect (increasing the number of GI events across the board) but rather may be due to specific drug-drug interactions. They suggest further study of this issue. These results are so counter-intuitive, they may be discounted by the panel as statistical noise.

(J.P. Morgan Securities or Chase Securities has acted as lead- or co-manager in an offering of securities for this company within the past three years.)

Additional information is available upon request.

EXHIBIT 16

Pharmacia Hasn't Shown Celebrex Safety Benefit, FDA Review Says

Washington, Feb. 6 (Bloomberg) -- Pharmacia Corp.'s Celebrex painkiller isn't significantly less likely to cause stomach problems than older, cheaper painkillers, a U.S. government review of a company study concluded.

The U.S. Food and Drug Administration review of a trial, designed to show that Celebrex was less likely to cause stomach bleeding, could mean problems for Pharmacia tomorrow when it asks an FDA advisory panel to support changes to the drug's label.

The reviewers said the study didn't show significantly fewer stomach problems in patients taking Celebrex, known chemically as celecoxib, than in those taking ibuprofen or diclofenac, two older medicines known as non-steroidal anti-inflammatory drugs, or NSAIDs. Only by looking at selected parts of the data -- a practice discouraged by the agency -- was the company able to show a benefit, the reviewers said.

''Celecoxib did not demonstrate statistical superiority to NSAIDs or either comparator with regards to the primary safety endpoint . . . at any point in the trial although there were trends that favored celecoxib,'' wrote James Witter, the FDA

medical officer that reviewed the data.

The review was prepared for tomorrow's meeting, where the panel will hear both the FDA's and Pharmacia's analysts of the study data. If the panel and agency support changing the drug's label, the company will be freer to claim the drug is safer than older drugs.

On Thursday, the panel will weigh whether data show that Merck & Co.'s Vioxx, Celebrex's biggest competitor, is safer than older drugs. Both Vioxx and Celebrex are members of a class of drugs known as Cox-2 inhibitors, which were designed to be easier on the stomach than older drugs.

--Brian Reid in Chicago, though the Washington newsroom (202) 624-1820 or brireid@bloomberg.net/jcn

The FDA has posted the briefing documents for the meeting on its Web site:
http://www.fda.gov/ohrms/dockets/ac/01/briefing/3677b1.htm

Story illustration: to graph the performance of Pharmacia shares against the Dow Jones Industrial Average over the past year, type

EXHIBIT 17

DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

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ARTHRITIS ADVISORY COMMITTEE

NDA 20-988/S009, Celebrex, (celecoxib, Searle)

Wednesday, February 7, 2001

8:00 a.m.

Holiday Inn Gaithersburg
Two Montgomery Village Avenue
Gaithersburg, Maryland

that is, endoscopic or radiographic proof of an evidence of an ulcer or a large erosion.

[Slide.]

Upper GI bleeding ulcers were the most common complication and were subcategorized into four categories again as prespecified by the protocol. Each category required the presence of a lesion.

There was either hematemesis with the lesion or the lesion demonstrated either active bleeding or evidence of recent bleeding, the presence of melena with the lesion, or the presence of blood in the stool by hemoccult testing along with some clinical evidence of substantial blood loss.

[Slide.]

Symptomatic ulcers were also defined in the protocol as any mucosal break with unequivocal depth found on a "for cause" work-up, that is, a work-up performed to investigate either a sign or a symptom of a potential ulcer complication. Again, all ulcer complications required hard documentation, that is, either endoscopic or radiographic documentation.

[Slide.]

I would like now to share with you the results of the trial, and I would like to direct my remarks first to GI outcomes and then to general safety outcomes.

In discussing with you the GI outcomes, I would

first like to describe the study population, the GI outcomes, and then potential sources of bias that may arise in assessing ulcer complications.

After discussions with the agency, we will focus today's discussion entirely on the entire study results as opposed to the six-month analyses that have been presented in the briefing documents.

[Slide.]

The demographics of the study population are shown here. Patients averaged 60 years in age and were predominantly female with the ethnic distribution as shown. Seventy percent of the patients had a primary diagnosis of OA and 30 percent a primary diagnosis of RA. No differences were seen between the treatment groups.

[Slide.]

In terms of the risk factors as defined by the MUCOSA trial, approximately 11 to 12 percent of patients were either 75 years or older, 1.5 percent had a prior history of GI bleed, and approximately 8 percent had a prior history of ulcer disease. Forty percent of the patients had a history of cardiovascular disease, again reinforcing my comment that cardiovascular disease is a common comorbidity in the arthritis patient population. No differences between treatment groups were observed.

[Slide.]

Aspirin was used by approximately 22 percent of the trial population, steroids were used by approximately 30 percent of the trial population, and anticoagulants, which were permitted, were used by approximately 1 percent of the trial population. No differences between treatment groups again were apparent.

Although over-the-counter NSAIDs were prohibited during the trial, approximately 5 to 6 percent of patients in each of the treatment groups used such over-the-counter NSAIDs, and in keeping with this being a real world clinical trial, such patients were not removed from the protocol, but were analyzed and kept within the study.

[Slide.]

Patients participated for a mean of approximately 7 months with a maximum exposure ranging between 12 and 15 months. Total exposure in the trial approximated 4,500 patient years split equally between celecoxib and the two NSAID comparators.

[Slide.]

I would like to characterize for you individually now the demographics of both the OA, as well as the RA cohort contained within this trial. OT patients on average tended to be slightly older than the overall study population and were predominantly female. These patients had long-standing OA of approximately 10 years in duration

and most had been on prior NSAID therapy up until the inception of the trial. Again there were no differences between treatment arms.

[Slide.]

The RA population within the trial tended to be younger, was still predominantly female, but had long-standing disease of approximately 10 years in duration. Most had used NSAIDs prior to the trial, and approximately 50 percent used steroids and/or methotrexate during the trial, and again there were no differences between treatment arms.

[Slide.]

In terms of the disposition of patients, approximately 50 percent or actually slightly less than 50 percent of patients completed the trial. Significantly, fewer patients assigned to the ibuprofen arm completed the trial compared to celecoxib patients.

More patients on diclofenac withdrew for adverse events compared to the celecoxib-treated patients, and more patients withdrew from the trial for treatment failure assigned to ibuprofen relative to celecoxib. No patients were lost to follow up that is, their medical status was ascertained at the time they exited from the trial, so no information is lacking because of lost to follow up patients.

[Slide.]

So, to summarize, this was a representative cohort of arthritis patients. Aspirin use was substantial, approximately 1 in 5 patients used aspirin. No information was lost because of lost to follow up patients.

Exposure to the study drugs was substantial and ranged up to 15 months. Moreover, there was a higher incidence of withdrawals seen from the study compared to celecoxib, in ibuprofen-treated patients for treatment failure, and diclofenac-treated patients for adverse events.

I would like now to discuss for you the GI outcomes of the trial.

[Slide.]

During the trial, 1,500 cases of potential ulcer complications were reported and each was evaluated by the committee. Forty-four of these cases were diagnosed as ulcer complications, 67 as symptomatic ulcers which did not meet the definition of ulcer complication, and the balance were assigned other diagnoses.

[Slide.]

In terms of the incidence of ulcer complications, there was no difference in comparing celecoxib to the NSAIDs combined as a group.

[Slide.]

In terms of the combined endpoint or the extended

endpoint, symptomatic ulcers and ulcer complications, there was a significant difference observed between NSAIDs and celecoxib with approximately a 40 percent reduction with a p-value as shown.

[Slide.]

The Kaplan Meier curves which form the basis of the prior bar graph are shown here. Again, there was a linear accrual of events throughout the duration of the trial with a p-value as shown here. This p-value is obtained from the log-rank test of the time-to-event.

[Slide.]

Because the comparison with NSAIDs was significant, we next compared with the individual comparators. There was no significant difference between celecoxib and diclofenac, but there was an approximately 2-fold reduction in the incidence of symptomatic ulcers and ulcer complications associated with celecoxib compared to ibuprofen with a p-value as shown.

[Slide.]

The Kaplan Meier analysis of this bar graph is shown here. Again, events accrued in a linear fashion throughout the trial in both treatment arms with the treatment difference being relatively easily apparent with a p-value of 0.017.

[Slide.]

with ulcers, most don't have symptoms.

So, for that reason, I agree with Byron, that the most objective parameter to really assess is what has been referred to as PUBs, the complicated ulcers, because those are indisputable, someone has a perforation or a bleed due to an ulcer, we know that is a clinically significant event. If someone has abdominal pain due to an ulcer, that person doesn't care if they have an ulcer or not, they are in pain whether they have an ulcer or not, so that is dyspepsia with or without an ulcer.

So, the question that is being asked here, have we really established, has the sponsor established clinically meaningful data which will allow us to conclude that there is a distinct safety advantage.

We heard two very different presentations today based on the data with very different analyses, very different conclusions. The onus of proof is on the sponsor to show that they are indeed different from the other agents.

After looking at the data presented, I can come to the conclusion that I can't conclude that at the present time, so I would have to say at the present time, from what I have seen, the upper GI toxicity we are talking about--and that is a question to ask--upper GI safety appears to be similar to those, to at least again to the different

presentations, I cannot say that it is different from the standard NSAIDs.

DR. WILLIAMS: I have just a little different interpretation on that. My conclusion would have been that I did think they showed a clinically meaningful and statistically difference from ibuprofen, but not from diclofenac, but these differences cancel out if they take aspirin at the same time, so that in the absence of aspirin, they do show a difference with one of the two NSAIDs, but not with the other, so I am not sure what that means in the totality of things.

I think they did show they were different than ibuprofen, but if you take aspirin on top of that, you can't cite any benefit.

DR. M. WOLFE: Again, the sponsors have said this is one study with two comparator NSAIDs. Therefore, putting the data together, I can't come up with a difference.

DR. WILLIAMS: I agree if you are going to combine both NSAID comparators together, you didn't see a difference, but I think if you look at the fact they had two comparators, they did show it with one, but not with the other.

DR. CRYOR: I think in trying to generalize this to a clinical population is we are not going to be able to predict which NSAID comparators patients are going to be on

I think the data doesn't necessarily show that today except I think there is an exception. I think as aspirin cancels out any benefits you expect to receive from specific COX-2 inhibition.

Now, the data did give me some hope in terms of ibuprofen, but I felt that the fact that we weren't able to show differences in diclofenac makes this so I can't generalize that in discussing it with all nonsteroidal anti-inflammatory drugs. Based on the data seen today, I can only tell them that versus ibuprofen.

DR. WOFSY: Dave Wofsy, also a rheumatologist from UC/San Francisco.

The challenge here for me is that it seems to me everybody is speaking truth. I agree with everyone who speaks. I agree with the sponsor and their emphasis, I agree with the FDA in their description, and I agree with everybody around the table who has spoken.

I think that is the dilemma here. It depends on which piece of this you pick out. So, let me simply say why I think that that is all so and how it translates into people with rheumatic diseases.

The primary endpoint wasn't met, it wasn't close to being met, so that is truth. The attempt to show that this is safer required retrospective redefinition of what the endpoints were and what the groups were, and that is

certainly less than compelling.

On the other hand, I do believe that the arguments that were made based on those retrospective analyses are very interesting and seriously point to the possibility, as Jim Williams has said, that in people who aren't taking aspirin and perhaps for certain nonsteroidal anti-inflammatory drugs, this is a safer approach with respect to GI toxicity.

I think that is strongly suggestive, not proven, and I don't think anybody here could really claim that it is proven given the manipulations, but I can't discount it.

I would also like to underscore two other things that were said by others that relate to this. The lack of any difference at all between the groups in overall serious safety problems, it seems to me to be a very important point. However you want to juggle these data, the patients in one group were no more or less likely to have something bad happen to them than the patients in the other group. I think I agree very strongly with the point that from the patient's point of view, that is key.

I also think it underscores a dilemma. The biggest dilemma for the sponsor, I don't know what to do with this, you have come forward with data that say, that strongly suggest to me that celecoxib has a GI advantage compared to one NSAID, but not compared to another.